Original Article

Selective arterial embolization of symptomatic and asymptomatic renal angiomyolipomas: a retrospective study of safety, outcomes and tumor size reduction

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Background: Angiomyolipoma (AML) is the most common renal benign tumor. Treatment should be considered for symptomatic patients or for those at risk for complications, especially retroperitoneal bleeding which is correlated to tumor size, grade of the angiogenic component and to the presence of tuberous sclerosis complex (TSC). This study reports our single-center experience with the use of selective arterial embolization (SAE) in the management of symptomatic and asymptomatic renal AMLs.

Methods: In this retrospective mono-centric study, all demographic and imaging data, medical records, angiographic features, outpatient charts and follow-up visits of patients who underwent prophylactic or emergency SAE for AMLs between January 2005 and July 2016 were reviewed. Tumor size and treatment outcomes were assessed at baseline and after the procedure during follow-up. Computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography was used to evaluate AML shrinkage. Renal function was measured pre- and post-procedure.

Results: Twenty-three patients (18 females, 5 males; median age, 45 years; range, 19–85 years) who underwent SAE either to treat bleeding AML (n=6) or as a prophylactic treatment (n=17) were included. Overall, 34 AMLs were embolized. TSC status was confirmed for 6 patients. Immediate technical success rate was 96% and 4 patients benefitted from an additional procedure. Major complications occurred in 3 patients and minor post-embolization syndrome (PES) in 14 patients. The mean AML size reduction rate was 26.2% after a mean follow-up was 20.5 months (range, 0.5–56 months), and only non-TSC status was significantly associated with better shrinkage of tumor (P=0.022). Intralesional aneurysms were significantly more frequent in patients with hemorrhagic presentation (P=0.008). There was no change in mean creatinine level after SAE.

Conclusions: SAE is a safe and effective technique to manage renal AMLs as a preventive treatment as well as in emergency setting, with significant reduction in tumor size during follow-up. A multidisciplinary approach remains fundamental, especially for TSC patients. In addition to size, the presence of intralesional aneurysms should be considered in any prophylactic treatment decision.

Keywords: Renal tumor; angiomyolipoma (AML); bleeding patient; arterial embolization; outcomes; therapeutic response

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Introduction

Angiomyolipoma (AML) is a benign renal tumor and the most common benign hamartomatous neoplasm accounting for 0.3% to 3% of all renal masses (1-3). They are more accurately characterized as perivascular epithelioid cell neoplasms (PEComas) in pathology (4). They are composed of fat, blood vessels and smooth muscle in varying quantities and are commonly divided into sporadic and non-sporadic groups (5,6). The sporadic group, accounting for approximatively 80% of all cases, consists of solitary lesion which occurs predominantly in middle-aged women with a prevalence of 0.22% to 0.29% in females and 0.02% to 0.1% in males (7-10). The non-sporadic group is related to tuberous sclerosis complex (TSC), an autosomal dominant multi-organ phacomatosis predisposing to benign tumor formation with activation of the mammalian target of rapamycin (mTOR) pathway, and is also more frequent in women (11). Within this group, AMLs develop in 50% of all patients during their life time, are often larger, multiple, bilateral, symptomatic and lesions are likely to widespread (7,8,12,13). TSC may also be associated with lymphangioleiomyomatosis, a progressive disease related to tuberous sclerosis, which usually affects the lungs of young women (14,15). Although a large majority of AMLs with focal epithelioid components are benign, pure epithelioid renal AML (EAML), a rare subgroup characterized by the presence of epithelial cells staining strongly for melanoma-associated markers, may become locally invasive and spread by affecting renal veins and inferior vena cava (16). Those aggressive epithelioid "carcinoma-like" variants are highly cellular with very little or no fat, tend to be larger and may become symptomatic for the majority (17,18).

As a benign lesion, most renal AMLs are asymptomatic, have a slow and consistent growth rate and minimal morbidity (19). They often do not require any intervention. However, they can cause flank pain or palpable mass but the main complications are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life threatening. The bleeding tendency is related to the angiogenic component of the tumor that includes irregular and/or aneurysmal blood vessels (20). The major risk factors for bleeding are tumor size, grade of the angiogenic component, and the presence of TSC (8,20). The European Association of Urology recommends active surveillance for most AMLs and treatment in case of pain, bleeding, or suspected malignancy. Prophylactic invasive procedures such as selective arterial embolization (SAE) and nephron sparing surgery (NSS) can be considered in large tumors, females of childbearing age as AMLs tend to grow in size and rupture during pregnancy because of their hormone sensitivity (21,22) and when access to emergency care may be inadequate (23). SAE can be used for prophylaxis of high-risk tumor, for acute management of tumor bleeding, or as a preoperative adjunct treatment for surgery to prevent intraoperative blood loss (8,20,24,25). This minimally invasive interventional radiology technique has become the primary treatment for AMLs since several years because it is less invasive than a surgical intervention and enables targeted treatment of bleeding vessels with a low risk of severe complications (20,24-41). The objective of this retrospective mono-centric study was to present our 11-year experience with planned prophylactic and emergency SAE of renal AMLs by reviewing our institution's series of 23 patients and evaluating complications, outcomes and tumor size reduction (TSR) after SAE.

Methods

Patients

All imaging studies and medical records of patients with AMLs treated with SAE in our institution were reviewed over an 11-year period between January 2005 and July 2016. An electronic search of our imaging database was performed and the initial patient list consisted of all report queries of patients treated at our hospital who matched for the words "angiomyolipoma(s)", "hemorrhage" and/or "embolization". From this first list, patients who underwent prophylactic or emergency SAE for AMLs with follow-up imaging and clinical follow-up were included. Patients without follow-up or who underwent arteriography without embolization were excluded of the statistical analysis; it concerned only the patients for whom another therapeutic strategy was decided and not because of a technical failure. EAMLs confirmed by histology were also excluded as this tumor has totally different components and behavior.

Demographic, clinical and biological data

We reviewed the medical records of all subjects and recorded demographic data (age and gender), AML type (sporadic or TSC-related), location and number of lesions, intervention type (prophylactic or emergency), clinical symptoms and complications before and within 4 weeks after SAE (according to the Society of Interventional Radiology classification system for complications) (42), recurrence (defined as recurrent symptoms or increase in tumor size of >2 cm on follow-up images requiring re-intervention) (27) and the need for further treatment independently of the reason. Serum creatinine levels were measured before SAE and during follow-up with Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) method for clearance calculation. TSC patients suitable for a trial with mTOR inhibitor (everolimus) were also considered.

Diagnosis, tumor size measurement and embolization technique

All AMLs were diagnosed with computed tomography (CT) and/or magnetic resonance imaging (MRI) on the basis of the presence of intra-tumoral fat without calcification or necrosis (43-45). Macroscopic fat appeared as areas with a density less than −20 Hounsfield units (HU) on non-enhanced CT or with cancellation of high signal intensity on T1-weighted MR images with fat saturation. In and opposed-phased chemical shift sequences were useful in low fat AMLs in which the aforementioned typical T1 findings were not readily apparent (46). Two cases were confirmed at histologic diagnosis after percutaneous needle biopsy because of lack of macroscopic fat within the lesion and one of them was an epithelioid variant.

Post-processing was performed on a syngo®.via workstation (Siemens Healthcare, Erlangen, Germany). All pre-SAE and follow-up images were reviewed by an experienced radiologist and each embolized tumor was measured using maximum diameter as previously applied in the literature (32,47). For measurement, we used the last available imaging exam performed before SAE (CT or MRI). Depending on availability, three-dimensional (3D) reconstructions with maximum diameter, 3D volume and density histograms calculation were performed for the prophylactic group diagnosed and followed-up with the CT modality by using MM Oncology software (Siemens Healthcare). Intralesional aneurysms were measured on angiographic images, not only with automatic calibration but also with reference to guiding catheter and microcatheter sizes. When a patient was found to have multiple aneurysms, the largest one was selected for evaluation.

The treatment plan was based on multidisciplinary proposal by interventional radiologists, urologists and/or nephrologists. SAE was performed under local anesthesia through the common femoral artery using 4–5 Fr angiographic catheters and coaxial microcatheters. An aortogram was first obtained to locate the renal arteries and to determine the presence of accessory renal arteries or extra-renal feeding vessels. After aortography, selective renal angiography was performed to assess AML circulation and extension of tumoral vessels outside the normal nephrogram, aneurysms, active extravasation and vascular displacements by the tumor or retro-peritoneal hematoma in emergency cases. Next, supra-selective catheterization of AML feeding vessels was performed using a coaxial microcatheter in order to spare as much renal parenchyma as possible. Various embolic materials were used alone or in combination as calibrated particles, liquid embolic agents and microcoils including: tris-acryl gelatin and polyphosphazene microspheres 100–700 μm (Embosphere®/EmboGold®, Biosphere Medical Inc.-Merit Medical Inc., Rockland, MA, USA; Embozene®, CeloNova-Boston Scientific, Marlborough, Massachusetts, USA), detachable microcoils (Detach-18®, Cook Medical Technologies LLC, William Cook Europe A/S; Interlock-18 Coil®, Boston Scientific Corporation), acrylic glue (N-butyl 2-cyanoacrylate, Glubran 2®, GEM Srl, Viareggio, Italy) mixed with ethiodized oil (Lipiodol® Ultra-Fluid, Guerbet, Aulnay-sous-Bois, France) in a 1:3 to 1:6 ratio, and Onyx® 18 (Covidien, Mansfield, MA, USA). One covered stent (Fluency® Plus Endovascular Stent Graft 7–40 mm, C.R. Bard, Inc., New Jersey, USA) was used to exclude a small bleeding adrenal branch from the origin of a renal artery in one patient. Embolic materials were injected under fluoroscopic guidance and coils were used to occlude large aneurysmal formations that would have been unsuitable for particle embolization alone. Additional supplying branches were selectively catheterized and embolized until total devascularization. Technical success was defined as stasis of flow in arteries feeding the tumor and lack of opacification of AML on post-SAE angiogram (35,41).

After the procedure, patients embolized for preventive

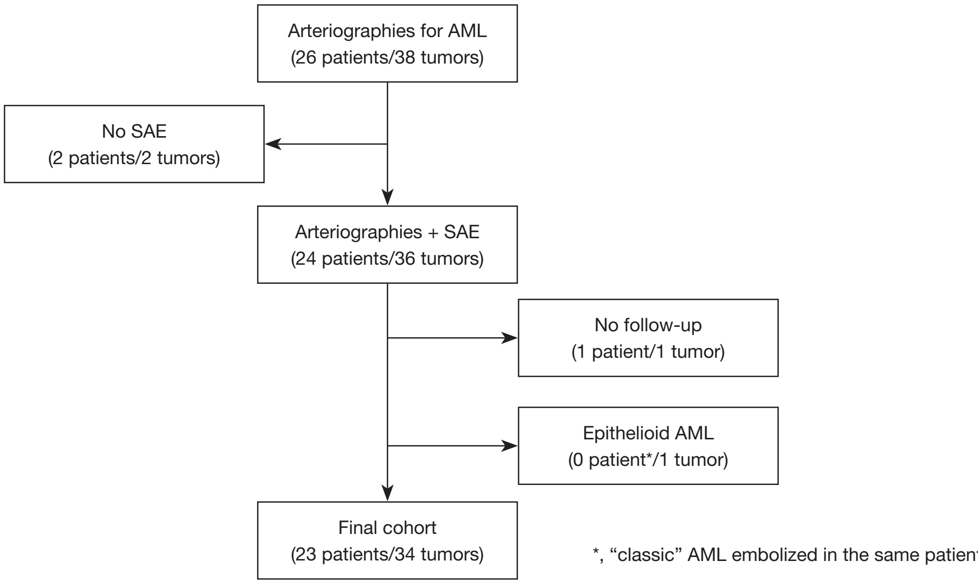

Figure 1 Flow chart of the study cohort. AML, angiomyolipoma; SAE, selective arterial embolization.

purpose were transferred to a urology department at our institution or in a referring hospital for 24–48 h stay and usually discharged the day after embolization. Vital signs were monitored and post-embolization syndrome (PES) (low-grade fever, pain and vomiting 3–7 days after SAE) routinely treated with non-steroidal anti-inflammatory drugs (NSAID). Antibiotic prophylaxis was not given. Patients from the TSC group were admitted to the nephrology department which was the best qualified to monitor them. Finally, patients embolized in emergency were then referred to various departments, especially intensive care and surgical units.

Follow-up

Medical records, outpatient charts, follow-up visits and imaging were reviewed. All the patients without follow-up at our institution were contacted by phone or e-mail to evaluate their current medical status and the need for additional treatment. They also provided their latest biology and imaging follow-up. Most of the outpatients underwent follow-up by the urology and nephrology teams 3–6 months after the procedure and once a year thereafter. CT or MR follow-up was recommended 3 months after SAE and annually if no change or decrease in size was noted. Images were obtained at different institutions with different equipments and protocols. For measurement, we used the last imaging exam available (CT or MRI or US).

Statistical analyses

Qualitative variables were described as percentages and compared using exact Fisher test. Quantitative variables were described using means with standard deviations (SDs) and medians with ranges. They were compared using the non-parametric Mann and Whitney test. Correlation between the tumor reduction and initial tumor size was determined using Pearson coefficient.

P values less than 0.05 were considered as significant. Analyses were performed using SAS® 9.3 (Statistical Analysis Software).

Results

Figure 1 represents flow chart of cohort construction for statistical analyses. The demographic and clinical data are presented in *Table 1*. During an 11-year study period, 23 patients underwent SAE in emergency to treat bleeding AMLs (n=6) (*Figure 2*) or as prophylactic treatment for high-risk AMLs (tumor size >4 cm, abnormal vasculature on CT, other symptoms) (n=17) and could be followed-up. One small sporadic asymptomatic AML was not embolized because its feeding vessels could not be identified during the arteriography; a percutaneous radiofrequency ablation was performed instead (48,49). We preferred a conservative approach by active surveillance for a second sporadic asymptomatic AML because of its very small

Table 1 Patient demographic and clinical data

Variables	Data
No. of patients	23
Gender, n [%]	
Male	5 [22]
Female	18 [78]
Age at presentation, years	
Mean ± SD	52±19
Median [range]	45 [19–85]
TSC status, n (%)	
Yes	6 (26.1)
No	17 (73.9)
Type of SAE, n (%)	
Prophylactic	17 (73.9)
Emergency	6 (26.1)
Indications, n (%)*	
Size only	13 (56.5)
Composition only**	1 (4.3)
Pain	7 (30.4)
Hematuria	4 (17.4)
Retroperitoneal bleeding	6 (26.1)
Type of AMLs, n (%)	
Unique	11 (47.8)
Multiple	12 (52.2)
Presentation of AMLs, n (%)	
Unilateral	14 (60.9)
Bilateral	9 (39.1)
Presence of aneurysms, n (%)	
Yes	8 (34.8)
No	15 (65.2)
No. of AMLs embolized	34
Type of AMLs, n [%]	
Tuberous sclerosis associated	17 [50]
Sporadic	17 [50]
Side of AMLs, n (%)	
Right	18 (78.3)
Left	16 (69.6)

*, possible multiple indications per patient; **, size <4 cm but (fat-poor AML) according to density histogram. TSC, tuberous sclerosis complex; SAE, selective arterial embolization; AMLs, angiomyolipomas; SD, standard deviation.

angiomyomatous component. One embolized patient was excluded because he died from heart failure before the first imaging control. We decided to treat a small epithelioid variant with SAE as this sub-group tends to be locally invasive and become symptomatic and another small AML on the same patient due to its high vascular composition (40,50). Additional percutaneous thermal ablation with microwaves was decided for the epithelioid variant because of its uncertain evolution. The first tumor was excluded from statistical analysis according to exclusion criteria (tumors, n=34) (*Figure 3*). One patient had a single right kidney before treatment. As it is widely accepted that lesions over 4 cm are more likely to become symptomatic (>90%) and more likely to bleed (>50%), almost all sporadic lesions were embolized on the basis of the size only (51).

AMLs were successfully embolized for 22 patients in the first instance (96%) with immediate and complete devascularization on post-procedural aortogram and 4 re-embolizations were necessary during the follow-up because of incomplete embolization (n=1) or recurrence (2 bleeding AMLs and 1 re-growth). Microspheres and glue were the most frequent embolic agents used. Aneurysms were found in eight tumors (*Figure 4*). In our cohort, total nephrectomy was performed for one renal AML 9 months after the primary treatment with SAE therapy because of poor functional parenchyma on follow-up.

Patient outcomes, follow-up times and changes in tumor sizes are presented in *Table 2*. The mean size of AMLs was 8.9 cm and the median size was 7.7 cm. Minor complications affected 14 patients with PES treated with conservative measures (n=14), persistent hematuria (n=1) and pyelonephritis (n=1). Major complications affected three patients with two renal abscesses formations 17 and 21 days after the procedure and one femoral false-aneurysm associated to renal abscess during hospitalization. Drainage of renal collections was proposed to the first and the second patient; they recovered well and were discharged after 1 week. A few days after embolization of femoral false-aneurysm and abscess drainage, the third patient unfortunately died from hemodynamic failure. One TSC patient deceased from tumoral brain hemorrhage 4 years after SAE and one patient from the sporadic AML group had a total contralateral nephrectomy for concomitant renal cell carcinoma (RCC). Recurrence affected three patients during follow-up and all of them were successfully re-embolized with good results. The efficacy of embolization was determined over a mean follow-up of 20.5 months (range, 0.5–56 months). No patients were lost to follow-

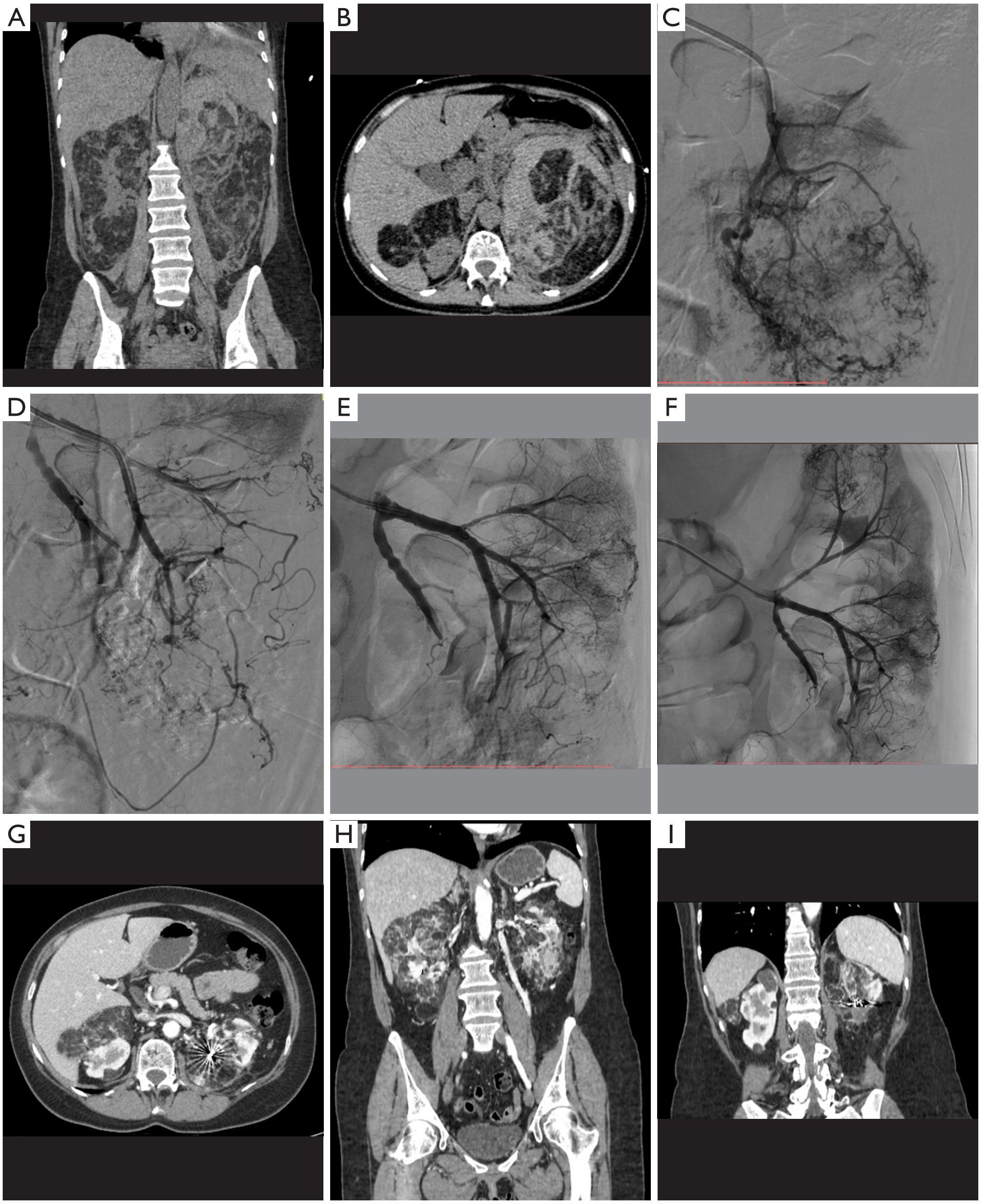

Figure 2 A 63-year-old woman with TSC, hospitalized for left acute flank pain, hematuria and deglobulisation. Unenhanced CT scan revealed three right AMLs and left perirenal hematoma whose origin was a giant left AML, with almost no recognizable renal tissue (A,B). Embolization to stop bleeding was performed urgently. Selective injection of four branches of the left renal artery showed diffuse perirenal hypervascularization with neovascularization and small vascular malformations (example of left lower branch presented) (C,D). Angiogram after selective embolization with microspheres (Embozene® 400 µm) showed good devascularization of the lower contingent. The persistent hypervascular contingents were treated in a second time (E,F). The three right AMLs were also treated in the same time with glue and microcoils. Four years after, CT-scan follow-up showed a total decreased in size of 11% of the three right AMLs with consistent viable renal parenchyma and no decrease of renal function. An average shrinkage of 17% of the left AML was also noted, without persistent perirenal collection (G-I). AML, angiomyolipoma; TSC, tuberous sclerosis complex; CT, computed tomography.

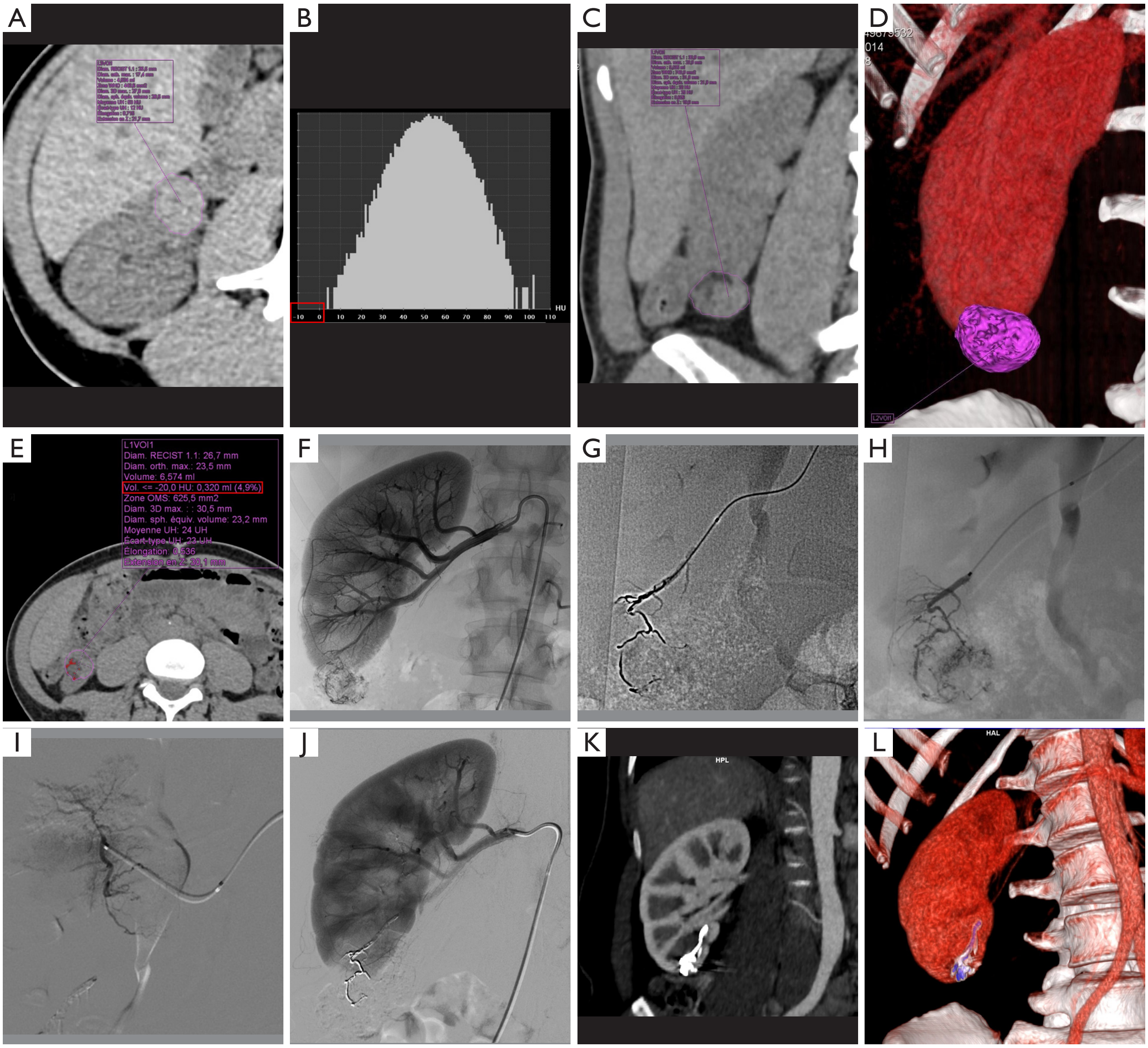

Figure 3 A 45-year-old woman with two small incidentally discovered angiomyolipomas in the right kidney. Biopsy of the first one in the medial pole confirmed an epithelioid variant without macroscopic fat component as shown in density histogram of unenhanced CT scan after tumors segmentation (A,B) and the second one in the lower pole had predominant angiomyomatous content with less than 5% of fat (C-E). An endovascular approach was decided. Right renal angiogram demonstrates middle and inferior pole AMLs (F). After selective embolization of the first AML with Onyx® (G,H) and the second one with a mixture of Glubran 2® and lipiodol (1:6) (I), post-procedure angiogram showed total devascularization of both tumors (J). Contrast-enhanced CT scan 8 months after embolization showed total atrophy of lower pole AML (K,L). Maximum diameter of epithelioid middle pole AML decreased by 21% and additional percutaneous thermal ablation with microwaves was decided because of its uncertain evolution. AML, angiomyolipoma; CT, computed tomography.

up. For measurement of tumor sizes before SAE, CT was used for 18 patients and MRI was used for 5 patients. For measurement of tumor sizes after SAE, CT was used for 15 patients, MRI was used for 6 patients and ultrasound was used for 2 patients. Seventeen patients had pre-existent reduction of glomerular filtration rate (GFR) with mild reduction for 13, moderate reduction for 3 and severe for 1 according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) classification for chronic kidney disease (CKD) (*Table S1*).

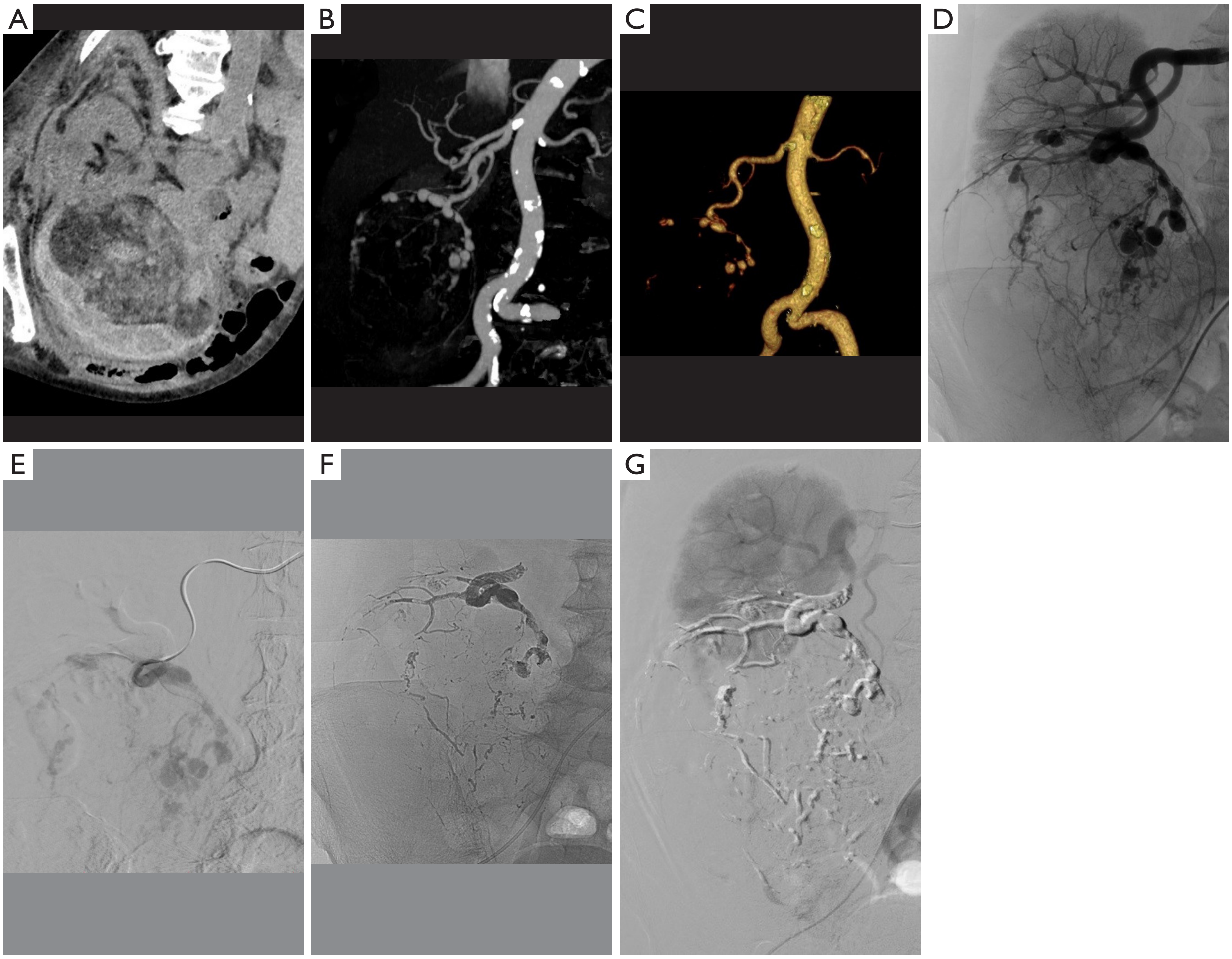

Figure 4 A 77-year-old woman hospitalized for right acute flank pain, hematuria and deglobulisation. Unenhanced CT scan revealed right perirenal hematoma caused by a giant right lower pole AML (A). Post-treatment maximum intensity projection (MIP) (B) and volume rendering (VR) (C) images of arterial phase CT scan revealed several clusters of aneurysms on the periphery of the mass. Embolization to stop bleeding was performed urgently. Selective injection of a lower branch of the right renal artery showed hypervascularization of AML with neovascularization and aneurysms (D). After selective embolization of AML with a mixture of 1:7 glue and lipiodol (E,F), post-procedure angiogram showed total exclusion of AML with good preservation of viable renal parenchyma (G). AML, angiomyolipoma; CT, computed tomography.

There was no change in creatinine mean level after SAE. Changes in AMLs size after SAE are summarized in *Table 3*; the mean AMLs size reduction was 2.1 cm (26.2%) (*Table 2*) and only non-TSC status was significantly associated with better shrinkage of the tumors (P=0.022).

Hemorrhagic presentation was significantly more frequent in patients with intralesional aneurysms (P=0.0086) (*Table 4*), with presence of aneurysms in 62.5% of patients embolized in emergency for hemorrhage and only one hemorrhagic case without aneurysm found on arteriography.

Discussion

Prior to 1976, more than 90% of sporadic AMLs were treated with total nephrectomy, as a malignant lesion could not be excluded (48). With improvement of cross sectional imaging and even in cases of low-fat tumors, AMLs can now be confidently diagnosed with an MRI specificity of up to 99% (52,53). Since the first report by Adler *et al.* in 1984 (54), transarterial embolization has increasingly been used to become the new standard for preventive or emergency treatment of AMLs with minimally invasive

Table 2 Outcomes, follow-up and changes in tumor sizes after SAE

Variables	Data
Size of AMLs before SAE, cm	
Mean ± SD	8.9±5.0
Median (range)	6.7 (1.0–20.9)
Size of symptomatic AMLs before SAE, cm	
Mean ± SD	12.4±7.2
Median (range)	11.1 (5.0–24.9)
Mean follow-up (range), months	20.5 (0.5–56.0)
Tumor size reduction	
Mean ± SD, cm	2.1±2.1
Mean rate ± SD, (%)	26.2±24.4
Renal function, mL/min/1.73 m^2	
Before SAE, mean ± SD	78±21
After SAE, mean ± SD	77±31
Technical success rate of first embolization*, n (%)	22 (95.6)
Need for re-embolization, n (%)	4 (17.4)
Recurrence**, n (%)	3 (13.0)
Increase in size on follow-up	1 (4.3)
Recurrent bleeding symptoms	2 (8.7)
Need for renal surgery post-SAE, n (%)	1 (4.3)
Minor complications***, n (%)	14 (60.9)
PES	14 (60.9)
Hematuria	1 (4.3)
Nephritis	1 (4.3)
Major complications***, n (%)	3 (13.0)
Puncture site false aneurysm	1 (4.3)
Abscess	3 (13.0)
Death	1 (4.3)
Embolic material used****, n (%)	
Microspheres	16 (69.6)
Cyanoacrylate glue	10 (43.5)
Microcoils	3 (13.0)
Onyx	2 (8.7)
Covered stent	1 (4.3)
Everolimus treatment, n (%)	
Yes	4 (17.4)
No	19 (82.6)

Table 2 (continued)

Table 2 (continued)

*, defined as stasis of flow in arteries feeding the tumor and lack of opacification of AML on post-SAE angiogram; **, defined as recurrent symptoms or increase in tumor size of >2 cm on follow-up images requiring re-intervention; ***, defined as complications within 4 weeks of SAE (according to the Society of Interventional Radiology classification system for complications) with possible multiple complications per patient; ****, possible multiple embolic materials per patient. AMLs, angiomyolipomas; SAE, selective arterial embolization; PES, post-embolization syndrome; SD, standard deviation.

selective targeting of small arterial feeders (25-27,36). Literature comparing nephrectomy and NSS with SAE in the management of AMLs is limited (3,8,55,56) with medical and economic analyses favoring embolization in symptomatic renal AMLs or AMLs at risk of complications. Endovascular therapy for AMLs has less postoperative morbidity (6.9%) compared to partial nephrectomy (12%), with minimal invasiveness and shorter hospitalization (54,57). It also allows rapid stabilization in cases of acute hemorrhage with optimal sparing of the normal renal parenchyma to maintain maximal renal function which is especially important in TSC patients. Surgery allows complete resection of the tumor and pathologic analysis to confirm diagnosis but remains quite difficult for AMLs in some cases with complex vascular anatomy, hilar location or for TSC-associated AMLs because of the multiplicity of the lesions (47). In the case of failure of primary or repeat SAE, nephron-sparing surgery might be considered (20,58). In our series, only one patient had surgical resection decided by urologists after successful SAE because of poor residual functional parenchyma.

Literature about laparoscopic and percutaneous ablative therapies for AMLs is also limited and largely restricted to small and asymptomatic tumors. Radiofrequency ablation series demonstrate good results with few to no retreatments, minor complications and no recurrences (median follow up of up to 45 months) (48,49). To date, we have performed six radiofrequency ablations for asymptomatic AMLs in our center and one of them was considered due to lack of

Table 3 Comparison of changes in AMLs size after SAE according to presentation, type of SAE, presence of symptoms and aneurysms

Variables	AMLs (n)	Size	Mean	SD	Median	Min.	Max.	P value
Sporadic	17	TSR	3.1	2.3	2.4	0.6	8.6	0.0220
		TSR rate	35.5	21.7	32.9	7.9	100.0	
TSC	17	TSR	1.2	1.4	1.3	–1.3	4.0	–
		TSR rate	16.9	24.0	16.1	–26.0	67.7	
Prophylactic	25	TSR	1.5	1.3	1.7	–1.3	3.7	0.8913
		TSR rate	25.9	26.7	28.0	–26.0	100.0	
Emergency	9	TSR	3.9	2.9	4.0	0.0	8.6	–
		TSR rate	27.1	17.9	26.2	0.0	52.1	
Symptomatic	15	TSR	1.4	1.3	1.7	–1.3	3.7	0.5671
		TSR rate	27.8	29.8	28.0	–26.0	100.0	
Asymptomatic	19	TSR	3.1	2.5	2.7	0.0	8.6	–
		TSR rate	24.2	16.0	26.2	0.0	52.1	
Aneurysms	8	TSR	2.5	2.8	1.5	–1.0	7.5	0.3101
		TSR rate	18.8	21.5	18.3	–18.9	48.4	
No aneurysms	26	TSR	2.0	1.8	1.9	–1.3	8.6	–
		TSR rate	28.4	25.2	28.6	–26.0	100.0	

TSR in cm, TSR rate in %. AMLs, angiomyolipomas; SAE, selective arterial embolization; TSR, tumor size reduction; SD, standard deviation; TSC, tuberous sclerosis complex.

Table 4 Relationship between AML hemorrhage and presence of intralesional aneurysms

Variables	Hemorrhage (n=6)	No hemorrhage (n=17)	P value
Presence of aneurysms (n=8)	5	3	0.0086
Absence of aneurysms (n=15)	1	14	

AML, angiomyolipoma.

abnormal vessels on arteriography. Reports for the use of cryoablation for AMLs are actually limited to small series (59-61).

In every case, discussion between interventional radiologists and urologists is essential to determine the optimal management. For many years, the threshold diameter for prophylactic treatment has been 4 cm (7,8,48) since Oesterling *et al.* (51) estimated that in lesions greater than 4 cm, 82–94% were symptomatic and 50–60% bled spontaneously. However, this historical threshold has since been discussed by authors recommending treatment for asymptomatic tumors larger than 6 (62) or 8 cm (8,63) as the rate of symptomatic AML >4 cm seems to have been over-evaluated in old series (64). Hocquelet *et al.* (40) identified the percentage of fat content before SAE as a predictive factor of volume decrease in their series with a volume reduction significantly more important for AMLs with less than 50% of fat than for those with more than 50% of fat (84% *vs.* 50%; P<0.00001). In their multivariate analysis, the best predictive model for volume decrease included only the percentage fat content (R^2=0.61; P<0.0001). Unfortunately, the small number of unenhanced CT scans available to calculate density histograms did not allow us to confirm this hypothesis. However, we believe that in addition to size, composition of AMLs should play an important role in the embolization indication and results because the angiomyogenic component is the main cause of bleeding complications and the target of embolization. Planché *et al*. (50) observed that the angiomyogenic components disappeared faster after embolization than the fatty components, and that "fat-poor" AMLs exhibited a larger volume reduction after SAE compared to "fat-rich" AMLs. In our series, we took into consideration the amount of angiomyogenic component and decided to embolize a "fat-poor" AML <4 cm with less than 5% of fat. It was the best result of our study with total disappearance of the mass on follow-up imaging (*Figure 2*).

In the same patient, we also decided to embolize an epithelioid AML diagnosed by pathology. This independent rare subtype of AML has malignant potential and imaging characteristics similar to RCC. Some cases of epithelioid AML metastasized to the lung, liver or bone have been previously reported but our patient wasn't metastatic and was asymptomatic (65-67). As the proper treatment for epithelioid AML is still discussed, we decided to perform an additional thermal ablation of the tumor while other authors recommend a more aggressive strategy using surgery with or without chemotherapy (68).

Several studies have recently recommended active surveillance as initial treatment for asymptomatic or mildly symptomatic AMLs, even if they are >4 cm (59). Ouzaid *et al*. (69) found that only 13 out of 38 patients with AML >4 cm discontinued active surveillance after 4 years mean follow-up, arguing that treatment for all tumors >4 cm would have resulted in a 65% over-treatment rate and that 67% of symptomatic patients were managed with active surveillance without complications. Bhatt *et al*. (64) found in their series of 447 patients up to 70% of asymptomatic lesions >4 cm with no difference in growth rates for lesions >4 and <4 cm. They support the hypothesis that a small sub-group of "fast growers" tend to be significantly more symptomatic than "slow" or "non-growers" and should be aware of the risk of progression and bleeding. Recent studies have suggested that although tumor size is important, size of associated aneurysms may be more significant. Yamakado *et al*. (27,70) found using the conventional cut-off of 4 cm has significantly poorer specificity (38%) than aneurysm of 5 mm or larger (86%) and aneurysm size was the only factor significantly linked to rupture in their multiple regression analysis (P=0.001). Aneurysms may be seen on CT scans but small ones are more easily assessed by conventional angiography (71). In our series, aneurysms were significantly more frequent in hemorrhagic patients (P=0.0086), confirming the importance of tumor composition.

A recent strategy for managing AML in patients with TSC is based on the use of targeted therapeutics focused on inhibition of the mTOR pathway to stop tumor progression and even promote regression of tumors. The first mTOR inhibitor tried was sirolimus, also known as rapamycin, initially developed as an immunosuppressive agent in solid organ transplantations. Everolimus is a rapamycin derivative that has been recently studied with data from two randomized controlled trials suggesting safety and efficacy (72,73). EXIST-2, a double-blind-randomized controlled trial that included 118 patients with 3 cm or larger AMLs in the setting of TSC, randomized everolimus and placebo (67). At a median interval of 38 weeks there was a 42% response rate for the everolimus group [95% confidence interval (CI), 31–53%] versus 0% for the placebo group (95% CI, 0–9%) with a response defined as a 50% or greater reduction in total AMLs volume. Median time to response for everolimus was 2.9 months and median exposure was 8.7 months. Progression-free rates for everolimus and placebo, respectively, were 92% (95% CI, 65–98%) and 25% (95% CI, 1–64%) at 12 months and no patients who achieved a response in AML volume reduction progressed. A longer-term analysis of everolimus treatment demonstrated stability of everolimus effects over time with an improvement in response rate to 54% (median exposure, 28.9 months) (74). AML shrinkage continued over time and no hemorrhage occurred. Six patients (5.4%) presented AML progression at any time of the study.

Four of the six TSC patients in our SAE series received everolimus and it is difficult to determine which treatment had the greatest impact on the change in tumor size. Among those patients, one patient presented a 17% increasing size of tumors (sum of maximal diameters) after a 56 months follow-up and the three others presented respectively a 36%, 44% and 13% shrinkage (49-, 36- and 1-month follow-up). The first patient had severe renal impairment before treatments with stage 4 CKD and unfortunately progressed to stage 5. The second patient had stage 2 CKD before treatments and progressed to stage 3 with one single kidney before any therapeutics whereas the third maintained stage 2 CKD. The fourth patient did not have any renal impairment before and after treatments. Severe renal impairments (GFR <30 mL/min/1.73 m^2) were observed in 7 (6.3%) patients at least once post-baseline in EXIST-2 trial but all of these patients had compromised renal function (GFR <60 mL/min/1.73 m^2) prior to everolimus initiation.

No patients had stage 3/4 elevated serum creatinine, but 15 (13.4%) patients had stage 1/2 elevations.

Though these trials suggest safety and efficacy of everolimus in decreasing AML tumor and preventing progression in TSC population, its role remains to be investigated. Indeed, there is no study to our knowledge comparing SAE and mTOR only treatment. Moreover, the role of mTOR in the management of non-TSC associated AML remains to be determined.

In our series, two TSC patients presenting large AMLs were managed with SAE only. A 13% and 15% decrease was respectively observed with stage 3 and 2 CKD before treatment. No CKD progression was noticed for the first patient and the second patient presented a surprising renal function improvement after SAE. We explain these changes by the fact that we used only two renal function values for reference: the last available value before treatment and the last available value during the follow-up. Renal clearance is a complex variable influenced by many exogenous and endogenous events and it is hard to determine whether the treatment or this multi-organ disease had the most influence on renal function in our limited study population. In their 16 TSC-patients-only AML embolization series, Williams *et al.* (30) found no statistically significant change in GFR after embolization with a mean interval between the procedure and the most recent renal function measurement of 23 months. Mean GFR before embolization was 95.75 mL/min/1.73 m^2. Their study suggest efficiency and safety of SAE to treat AML in TSC patient by preserving renal function which is very important in this population but the evolution of GFR seems to be uncertain once it has begun to deteriorate. Villalta *et al.* (39) found no difference in tumor reduction size in patients with or without TSC. We observed significantly better tumors shrinkage in non-TSC patients after SAE (P=0.022) than in TSC-patients, suggesting the importance of combining different therapeutic strategies to obtain similar results in TSC patients.

We encountered low complication rates as it has been described in the past series (*Table S2*). Only three patients presented severe complications. One false-aneurysm of the common femoral artery was successfully embolized and three abscesses formation following necrosis and liquefaction of tumors after SAE were managed with percutaneous drainage (75). As expected, PES, an inflammatory response causing pain and fever that can last for several days following SAE, was the main minor complication. Every patient pain and/or fever was easily managed with analgesics. Bissler *et al.* (76) described the use of a short-term tapering dose of prednisone over a 2-week period after SAE of AMLs instead of acetaminophen and it appeared to reduce PES and improved patient comfort.

Since Han *et al.* (24) and Lee *et al.* (25) mostly used iodized oil mixed with absolute ethanol in their 90's series, many authors adopted this approach until Rimon *et al.* (13) reached a 94% clinical success rate by adding polyvinyl alcohol (PVA) at completion. In our series, we used various embolic agents since studies comparing smaller and larger embolic agents for AMLs embolization did not find difference in tumor reduction size or need for repeat embolization (39). However, we're using more and more N-butyl 2-cyanoacrylate glue (Glubran 2®) for SAE these last years. Property of glue for arterial occlusion is mostly seen in lesions supplied by end-arteries; as a consequence, intra-parenchymal tumors or vascular lesions with end-artery feeders such as AMLs are suitable for glue application, with the expectation of a sclerosis of the tumor and a total devascularization of the vascular bed (77). Advantages of glue are that it works instantly, provides fast and distal embolization with high dilution of lipiodol (ratio, glue:lipiodol >1:5), completely occludes vessels and is permanent (78). It is also cheap and easy to use mixed with ethiodized oil (lipiodol), making easier to see the progression of glue in the vascular feeders and to visualize reflux along the microcatheter, which can reduce the risk of gluing the tip of the microcatheter and injecting glues into normal renal parenchyma. No series have described the use of glue in such a setting whereas it combines many advantages over other embolic agents, even if a learning curve is mandatory.

This study has some limitations. First, this is a retrospective study with a small size cohort due to the rarity of large and/or symptomatic AMLs. Our population was heterogeneous with sporadic cases (n=17), TSC patients (n=6) and different presentations (preventive *vs.* emergency embolization). Second, as in other studies, we encountered difficulty to measure with accuracy large AMLs associated with retroperitoneal hemorrhage, especially as several modalities were used (US, CT and MRI). In particular, data were difficult to measure in cases of AML ruptures, which was often the mode of revelation of emergency cases. In addition, the follow-up images of some patients were obtained from other hospitals with different equipments than that available in our hospital. However, no patients were lost during follow-up in this study. Variable follow-up [mean follow-up of 20.5 months (range, 0.5–

56 months)] should not impact the findings of our study since the majority of AMLs shrinkage occurs within the first years following SAE (79). This was confirmed for the last two patients of our series with only short term follow-up images available; the first one presented a 8% and 9% tumors shrinkage 1 month after treatment and the second an impressive 48% decreased 2 months after embolization. With 13% of complications, 13% of recurrence and 17% of repeated embolization, our results are comparable to those previously reported in the literature and summarized in *Table S2*.

Conclusions

SAE is an effective technique to manage AMLs preventively or in emergency to treat bleeding, with substantial reduction in tumor size, low recurrence rates and acceptable complications. We found a larger tumor reduction size for sporadic AMLs, stressing the importance of a multidisciplinary approach to AMLs associated to TSC which are usually bigger, multiple and consequently harder to manage. This study emphasizes the role of tumor composition and especially the presence of intratumoral aneurysms which was significantly more frequent in hemorrhagic tumors. As a consequence, we believe that in addition to size, the initial composition of the tumor should be considered in treatment decision. Further studies are needed to clarify the precise role of all therapeutic modalities currently available, especially in TSC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ⇑ GFR	≥90
2	Kidney damage with mild ⇓ GFR	60–89
3	Moderate ⇓ GFR	30–59
4	Severe ⇓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities in blood or urine tests or imaging studies. GFR, glomerular filtration rate.

Table S2 Results of contemporary selective arterial embolization series for AMLs

Series	Year	No. of patients	Mean tumor size (cm)	No. of complications (%)*	Recurrent hemorrhage or growth (%)	No. of repeat embolization (%)	No. of surgery (%)	Mean follow up (months)
Han *et al.*	1997	14	11.0 (range, 4.0–35.0)	0	4 (28.60)	2 (14.3)	1 (7.1)	33.0
Lee *et al.*	1998	15	8.5 (range, 6.0–15.0)	1 (6.70)	3 (20.00)	2 (13.3)	NA	35.6
Ewalt *et al.*	2005	16	NA (range, 4–21)	2 (12.50)	0	2 (12.5)	NA	NA
Kothary *et al.*	2005	19	NA	0	6 (31.60)	6 (31.6)	NA	51.5
Rimon *et al.*	2006	17	10.0 (range, 5.5–20.0)	0	1 (5.80)	11 (64.7)	1 (5.9)	22.4
Dabbech *et al.*	2006	34	7.8 (emergency, range, 4.5–18.0); 5.3 (preventive, range, 4.0–11.0)	10 (29.40)	7 (20.60)	4 (11.8)	12 (35.3)	21.0
Williams *et al.*	2006	16	Vol. 314.99 cm^3 (range, 27.83–814.43 cm^3)	3 (18.75)	1 (6.25)	NA	NA	40.0
Lenton *et al.*	2008	17	NA	NA	5 (29.40)	5 (29.4)	NA	NA
Lee *et al.*	2009	11	8.57±2.66	1 (9.10)	2 (18.20)	1 (9.1)	1 (9.1)	28.2
Ramon *et al.*	2009	41	10.3 (range, 10.0–25.0)	8 (19.50)	16 (39.00)	15 (36.6)	3 (7.3)	57.6
Sooriakumaran *et al.*	2010	19	12.5 (range, TSC–median size)	3 (15.80)	8 (42.10)	NA	NA	NA
Tillou *et al.*	2010	21	NA (range, 2.0–13.0)	2 (9.50)	0	1	7 (33.3)	53.2
Bishay *et al.*	2010	16	15.0 (range, 10.0–25.0)	2 (12.00)	3 (18.80)	9 (56.3)	0	29.0
Chick *et al.*	2010	34	11.9 (range, 4.0–30.0)	1 (2.90)	5 (14.70)	2 (5.9)	2 (5.9)	44.2
Chan *et al.*	2011	27	10.9 (range, 4.0–30.0)	0	6 (22.20)	4 (14.8)	4 (14.8)	85.2
Stoica *et al.*	2011	20	8.2±2.8 (emergency); 5.2±2.2 (preventive)	0	3 (15.00)	2 (10.0)	1 (5.0)	NA
Villalta *et al.*	2011	48	7.8±5.9 (small); 8.5±4.4 (large)	5 (10.40)	14 (29.20)	14 (29.2)	1 (2.1)	14.0 (small); 29.0 (large)
Hocquelet *et al.*	2014	19	Vol. 136±174 mL	2 (10.50)	2 (10.50)	2 (10.5)	0	28.0 (median)
Duan *et al.*	2015	25	12.42±5.48 (23 patients)	2 (8.00)	1 (4.00)	0	2 (8.0)	50.2
Current series	2016	23	8.9 (range, 2.8–24.9)	3 (13.00)	3 (13.00)	4 (17.0)	1 (4.0)	20.5

*, except post-embolization syndrome. NA, not available; TSC, tuberous sclerosis complex; Vol., volume; AML, angiomyolipoma.