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Tumor necrosis after preventive embolization of large renal angiomyolipomas

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KEYWORDS
Angiomyolipoma; Embolization; Preventive; Necrosis

Abstract
Objectives: The purpose of this study was to retrospectively evaluate tumor necrosis following preventive embolization in patients with renal angiomyolipoma (RAML) at high risk of bleeding.

Patients and methods: Arterial embolization was performed in 24 patients (22 women, 2 men; mean age, 43 ± 13 years) with a total of 30 RAMLs (mean volume, 137 cm³ ± 163) between 1996 and 2012. Two sub-groups of patients were identified and further compared based on the presence or not of necrosis following arterial embolization.

Results: The technical and clinical success rates of arterial embolization of RAMLs were 97% and 87%, respectively. The mean initial volume of RAMLs differed between the two sub-groups with 331 cm³ in the group with tumor necrosis and 88 cm³ in the group without tumor necrosis (P=0.0047). High-fat content RAMLs were predominantly observed in the necrosis group and the mean volume reduction observed for high-fat RAMLs was 65% whereas it was 36% for low-fat content RAMLs. The six patients who developed RAML necrosis had arterial embolization using microspheres (one patient with microspheres alone and five with a combination of microspheres and metallic coils). All necrotic RAMLs displayed arterial dysplasia.

Conclusion: The risk of tumor necrosis is higher for larger RAMLs. The role of distal arterial embolization with microspheres in tumor necrosis in RAML is suggested by the results of our study but could not be definitely demonstrated statistically due to the limited sample size.

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Abbreviations: RAML, renal angiomyolipoma; TSC, tuberous sclerosis complex; MRI, magnetic resonance imaging.

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Introduction

Renal angiomyolipomas (RAMLs) are hypervascular benign tumors that convey a risk for hemorrhagic complications. They occur sporadically in 80% of patients or for the remaining in patients with tuberous sclerosis complex (TSC, 20%). In most cases, AMLs show tissue heterogeneity (vascular, adipose and muscle tissue) [1–7]. This category of lesion is rare, representing 1% of renal tumors, with an incidence ranging from 0.07 to 0.3% [8,9].

The treatment of acute bleeding due to rupture of RAML is well established depending on the patient’s hemodynamic status. Arterial embolization is currently used as the favored method [10–12].

However, no clear consensus has been reached on when and how to apply preventive treatment. The use of therapeutic arterial embolization is debated, depending on the risk of hemorrhage using criteria described in previous reports: tumor size > 4 cm, aneurysm > 4–5 mm, history of minor RAML bleeding [6,11,13]. When preventive treatment is indicated, surgery can be a valid approach if embolization fails or in some specific cases (isolated RAML, RAML with a large exorenal component, foreseeable difficulties in post-embolization follow-up) [14,15].

Several studies have demonstrated the technical and clinical efficiency of hemostatic and preventive arterial embolization [16–18]. Complications occurring after preventive arterial embolization, such as tumor necrosis, are generally rare [10].

The purpose of the present study was to describe the clinical, biological and imaging features of the main complication (i.e., tumor necrosis, as defined by lipid necrosis of the entire RAML) and to assess the risk factors involved in its occurrence.

Patients and methods

This retrospective single-center study covered a period of 16 years (from 1996 to 2012) and included 33 patients who underwent RAML embolization because of a potential risk of hemorrhagic complications (tumor size > 4 cm, aneurysm > 4–5 mm, history of minor AML bleeding). Only patients fulfilling the inclusion criteria for preventive arterial embolization were included; nine patients were excluded following emergency arterial embolization due to active bleeding with hemorrhagic shock.

Two patient sub-groups were identified following data collection based on the presence or not of post-embolization necrosis (Table 1). Creatinine clearance levels were evaluated prior to arterial embolization.

Imaging findings

Diagnosis of RAML was based on the presence of intratumoral macroscopic fat with a spontaneous attenuation value of less than −20 HU on computed tomography (CT).

The fatty component was considered to be predominant if an attenuation value < −20 HU was found in more than 50% of the tumor volume with only attenuation values < −20 HU. This 50% threshold was proposed by Planché et al. [19].

Clinical, biological and radiological follow-up was performed either by abdominal CT scans, or by a combination of CT scans and renal MR imaging examinations. Follow-up visits were scheduled six months after arterial embolization and then every two years. Patients in the necrosis group were monitored more regularly during the first year after embolization.

Selective embolization

Renal angiograms were first obtained via a puncture of the femoral artery using a 4- or 5-Fr introducer sheath. The aim was to achieve selective catheterization in order to preserve the maximum volume of the normal renal parenchyma.

Embolic agents consisted of microspheres, coils or a combination of metallic coils and microspheres.

Post-embolization assessment

The success of arterial embolization was assessed immediately using angiography and considered successful if the tumor vascular network, intratumoral aneurysms and arterial dysplasia were no longer visible.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics and RAML characteristics of the study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Overall population</td>
</tr>
<tr>
<td>Number of patients (n [%])</td>
<td>24</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43 ± 13</td>
</tr>
<tr>
<td>Male (n [%])</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Female (n [%])</td>
<td>22 (92)</td>
</tr>
<tr>
<td>Sporadic RAML (n [%])</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Congenital TSC lesions (n [%])</td>
<td>9 (37)</td>
</tr>
<tr>
<td>Number of RAMLs (n [%])</td>
<td>30</td>
</tr>
<tr>
<td>Mean initial volume of RAML (cm³)</td>
<td>137 ± 163</td>
</tr>
<tr>
<td>Mean aneurysm size (mm)</td>
<td>4.7 ± 5.8</td>
</tr>
<tr>
<td>Presence of arterial dysplasia (n [%])</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Number of predominantly fatty RAMLs &gt; 50% (%)</td>
<td>24 (80)</td>
</tr>
<tr>
<td>Number of RAMLs with aneurysm (%)</td>
<td>14 (47)</td>
</tr>
</tbody>
</table>
Pre- and post-embolization RAML volumes were calculated using the ellipsoid formula in all three planes (one half the product of the three dimensions); the maximum change in volume was calculated using the last tumor measurements available on CT data.

Embolization procedures and data on the variation of RAML volume were reviewed for the whole study population, and then by subgroup (RAMLs treated with both coils and microspheres, with microspheres alone, and with coils alone). RAML volume variation was also analyzed depending on RAML fat content (over or under 50%) and the occurrence of post-embolization necrosis (Table 2).

Any post-embolization complications (Table 3) were recorded and classed based on the time of occurrence (postembolization syndrome, late tumor necrosis, early and late complications).

### Statistical analysis

Statistical analysis was performed using SAS\textsuperscript{®} v9.3 software (Cary, NC, USA). Continuous variables were described as medians, means and standard deviations (SD). Comparisons were performed using Chi² test or Fisher's exact test. Binary variables were described as raw numbers, proportions and frequencies. Comparison between the two subgroups of patients (depending on the presence of necrosis in RAML after arterial embolization) was performed using the Wilcoxon test.

### Results

Descriptive statistics and tumor characteristics are provided in Table 1 for the overall population and the two subgroups.

Twenty-four patients (22 women and 2 men) with a mean age of 43 ± 13 years (range: 15–77 years) were included in the study. They had a total of 30 embolized RAMLs.

RAMLs were sporadic in 15/24 patients (63%; of them 12 patients had a single RAML) or associated with tuberous sclerosis complex in 9/24 patients (37%) (all with multiple RAMLs). A single RAML was present in 11/24 patients (46%) and 13/24 patients (54%) had multiple RAMLs.

Twelve RAMLs were detected incidentally in the absence of bleeding. Eighteen RAMLs (60%) were diagnosed following lower back pain due to intratumoral hematoma or minor untreated hematoma (n = 11/18), including two pregnant women with light bleeding.

Prior to treatment, the mean RAML size was 7 ± 3 cm (range: 4–16 cm) and the mean pre-embolization volume was 137 cm\(^3\) (6–612 cm\(^3\)). Twenty-seven RAMLs (90%) were > 4 cm, 14 (47%) showed one or more aneurysms > 4 mm (as defined by the longest axis measured on CT scan) with a mean aneurysm size of 4.7 mm (ranging from 4 to 25 mm), 25 (83%) displayed arterial dysplasia and 24 RAML (80%) had a fat content > 50%.

Renal function prior to embolization was normal for all patients, as estimated by creatinine clearance levels.

A 2.7 Fr microcatheter was used for 27 RAMLs (90% of the tumors) and a 2.4 Fr microcatheter for the three remaining

<table>
<thead>
<tr>
<th>Population</th>
<th>Overall population</th>
<th>Without necrosis</th>
<th>With necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of RAMLs (%)</td>
<td>30</td>
<td>24 (80)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Distal embolization (microspheres) (n [%])</td>
<td>22 (73)</td>
<td>16 (67)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Proximal vessel occlusion (coils) (n [%])</td>
<td>27 (90)</td>
<td>22 (92)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Embolization with microspheres and coils (n [%])</td>
<td>18 (60)</td>
<td>12 (50)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Embolization with microspheres alone (n [%])</td>
<td>4 (13)</td>
<td>3 (13)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Embolization with coils alone (n [%])</td>
<td>8 (27)</td>
<td>8 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Number of successful procedures as assessed by angiography (%)</td>
<td>29 (97)</td>
<td>23 (96)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Mean duration of follow-up (months)</td>
<td>42 ± 36</td>
<td>49 ± 36</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>Mean reduction in RAML volume (%)</td>
<td>60</td>
<td>53</td>
<td>81</td>
</tr>
<tr>
<td>Mean reduction in RAML volume (%) for each embolic agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coils + microspheres</td>
<td>68</td>
<td>65</td>
<td>77</td>
</tr>
<tr>
<td>Microspheres alone (n [%])</td>
<td>1: 50</td>
<td>31</td>
<td>99 (n = 1)</td>
</tr>
<tr>
<td>Coils alone (%)</td>
<td>1: 12</td>
<td>1: 99</td>
<td>1: increase</td>
</tr>
<tr>
<td>Mean reduction in tumor volume (%) depending on fat content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fat &lt; 50%</td>
<td>36</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>fat &gt; 50%</td>
<td>65</td>
<td>57</td>
<td>81</td>
</tr>
<tr>
<td>Number of re-embolization procedures (%)</td>
<td>4 (13)</td>
<td>4 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial nephrectomy (n [%])</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
RAMLs. The embolic agents used were microspheres and/or coils. The embolization procedures included 22 (73%) distal embolizations using microspheres with size ranging from 200 to 1200 µm, and 27 (90%) proximal vessel occlusions with coils. Eighteen RAMLs (60%) were treated with a combination of microspheres and coils, eight (27%) with coils alone, and four (13%) with microspheres alone.

The mean duration of follow-up was 42 ± 36 months in the overall population (both sub-groups). Imaging follow-up consisted predominantly of abdominal CT scans (alternating CT scans and renal MR imaging in nine patients).

**Success rate of primary embolization and secondary treatment**

The technical success rate, as defined by uncomplicated arterial embolization and devascularization of RAML on arteriogram, was 97% (29/30). Embolization was not achieved in one patient due to arterial spasm during the procedure.

The clinical success rate, as defined by a decrease in RAML volume and vascularization (or even complete disappearance of the RAML during follow-up) was 87% (26/30 RAMLs) (Fig. 1).

Clinical success was only partial in four patients. Three of these four patients were re-embolized due to an increase in RAML size. The remaining patient underwent re-embolization for persistent hypervascularization during follow-up.

Following discussion by a multidisciplinary team of specialists (uroplogists and radiologists), nephrectomy was performed in one patient initially treated with microspheres and coils due to an increase in RAML size.

No active bleeding occurred during or immediately after re-embolization procedures. No cases of renal failure were observed immediately after the procedure or during follow-up. Transitory post-embolization syndrome with onset of fever and pain was observed in the days following the procedure in 19 patients (63%) and was managed with an appropriate analgesic treatment [20,21].

**Tumor necrosis**

Six (20%) of the 30 embolized RAMLs showed post-embolization tumor necrosis.

Tumor necrosis, defined as lipid necrosis of the whole RAML, differs from post-embolization syndrome by its delay (> 1 month after embolization) (mean delay of 2.3 months: four months [n = 1], three months [n = 2], two months [n = 1] and one month [n = 2]).

Post-embolization necrosis was characterized by specific clinical and biological features: chronic diffuse lower back pain often described as a nagging pain or heaviness,
persistent inflammatory syndrome (average duration of nine months ranging from one month to 18 months), and high CRP levels without any signs of infection.

In these six tumor necrosis cases, very similar imaging findings were observed: initial increase in volume due to necrosis and the subsequent inflammatory reaction (peri-renal or retroperitoneal), complete devascularization of the tumor, initial heterogeneous necrosis with air bubbles in the central part delimited by a thick, contrast-enhanced wall. This feature tends to gradually turn into a liquefactive fatty necrotic layer ("fat-necrosis level") (n = 6) (Figs. 2 and 3). Three patients showed pyelocalicial dilatation due to peri-renal inflammation, but no urinary derivation (stent) was needed because there were no significant signs of obstruction.

Drainage was performed in two patients due to a high risk of rupture of the necrotic tumor (retroperitoneal compartment extension and poor inflammatory clinical tolerance). One case was managed surgically (heterogeneous nature of the necrotic tissue) and the other percutaneously (important spread). In both cases, the outcome was favorable.

The mean size of necrotic RAMLs was 11 cm (7–16 cm) before treatment and 16 cm (9–27 cm) at the onset of necrosis. The lesions were surrounded by a thick capsule with a mean width of 10 mm (6–15 mm).

Subsequent to necrosis and the inflammatory reaction, the mean reduction in size of necrotic lesions was 81% (post-drainage for two lesions) with a mean size of 4 cm (1.5–9 cm).

Other events were also observed in the necrosis group: lipiduria (n = 3) was observed in three patients and two patients showed systemic inflammatory disease (one case of rheumatoid purpura several months after embolization and one case of inflammatory-like joint pain one year after embolization). However, the relationship between these clinical manifestations and the onset of necrosis was not fully established.

Comparison of the necrosis and non-necrosis sub-groups

All the patients in the sub-group with post embolization necrosis (n = 6) were women; the mean age was 41.5 years (25–54 years) (Tables 1–3). Two patients from this sub-group had tuberous sclerosis complex.

Arterial dysplasia was observed in all of the lesions of the necrosis sub-group (100%) and in 79% of non-necrotic lesions.

Figure 2. a: early phase angiography of a large RAAL in the lower pole of a right kidney showing arterial dysplasia (white arrow); b: contrast-enhanced CT scan in the axial plane obtained during the arterial phase of a large RAAL in the lower pole of a right kidney showing post-embolization (coils and microspheres) tumor necrosis. Fatty fluid layer (white arrow); c: fat-suppressed T1-weighted MR image after intravenous administration of gadolinium chelate during the nephrographic phase shows RAAL necrosis (white arrow) following arterial embolization with coils and microspheres of a large, high fat content RAML in the lower pole of a right kidney. Dilatation of the pelvicalyceal cavities (black arrow) by compression of the renal pelvis by the necrotic RAML; d: CT-guided drainage of large necrotic RAML in the lower pole of right kidney following arterial embolization with coils and microspheres.
There was a significant difference between the mean initial volume of the RAML in the necrosis sub-group (331 cm³) and the sub-group without tumor necrosis (88 cm³), as determined by the Wilcoxon test \((P = 0.0047)\) (Fig. 4).

High fat content RAMLs were more frequent in the necrosis sub-group (6/6 patients, 100%) than in the sub-group without tumor necrosis (18/24, 75%).

The mean post-embolization volume was 43 ± 41 cm³ for non-necrotic RAMLs and 30 ± 61 cm³ for necrotic RAMLs, although the difference between the two sub-groups was not significant \((P = 0.146)\). The mean reduction in tumor volume was 68% and 37% for patients treated with a combination of microspheres and coils \((n = 18)\) and coils alone \((n = 8)\), respectively. The results were variable for patients embolized with microspheres alone \((n = 4)\).

The reduction in tumor volume was therefore greater in the group embolized with coils and microspheres (68%) than in the group embolized with coils alone (37%). However no cases of necrosis were observed in the group embolized with coils alone.

The mean reduction in tumor volume (%) in the overall patient population was 60% (ranging from 0 to 100%). The reduction in tumor volume differed between the sub-groups with low fat content RAMLs (36%) and high fat content AMLs (65%). In the sub-group with high fat content RAMLs, this percentage was found to vary again depending on whether the RAML became necrotic (81%) or not (57%).

The other post-embolization complications reported in Table 3 (arterial hypertension, localized infarction) were not associated with tumor necrosis.

**Discussion**

Although its histopathological features are benign, 17–20% of all cases of peripheral bleeding are due to the rupture of dilated blood vessels in RAML [12].

The risk of RAML bleeding complications depends on several factors such as AML size (> 4 cm), intratumoral arterial aneurysms with diameters > 4 mm, intratumoral

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**Figure 3.** a: contrast-enhanced CT scan in the axial plane obtained during the arterial phase shows large RAML with arterial dysplasia (white arrow); b: early phase renal angiography of large RAML in the lower pole of a right kidney with arterial dysplasia (white arrow); c: early phase renal angiography: embolization with coils and microspheres of large RAML with arterial dysplasia (black arrow); d: contrast-enhanced CT scan in the nephrographic phase shows RAML necrosis following embolization with coils and microspheres of a large RAML with arterial dysplasia and a fatty fluid layer (white arrow); e: contrast-enhanced CT scan in the axial plane shows 90% reduction in RAML volume 12 months after arterial embolization (white arrow).
Different embolic agents have been described in the literature such as polyvinyl alcohol particles, ethanol, microspheres, gelfoam and coils [10,17,18]. However, previous studies using the same embolic agents as used here (i.e. microspheres and coils) did not assess the complications observed for each embolic agent [10,17,18]. Recent guidelines recommend the use of microspheres with a diameter of more than 500 μm to avoid leakage through intratumoral arteriovenous shunts [14,15,28].

Six cases of post-embolization tumor necrosis led us to search for factors that predispose to this complication by comparing the sub-groups with and without necrosis. This complication, which shows a unique imaging signature, is rarely described in the literature but has important clinical and biological consequences and can require surgical drainage. We identified the following predisposing factors:

- initial tumor volume: in our population, necrosis was observed in much larger tumors. The significant difference seen in tumor size reduction (P = 0.0043) is thus related to the initial volume of the RAML;
- fat content: all necrotic RAMLs had a high fat content (>50%). However 19 non-necrotic RAMLs also had a high fat content so, due to the limited number of patients included, it is difficult to demonstrate a statistical relationship between the fat content and the onset of necrosis;
- arterial dysplasia: all necrotic RAMLs displayed arterial dysplasia (Fig. 4);
- embolic agents: in both of the sub-groups in our population, RAML embolization was performed using microspheres, coils or a combination of both. However, all patients with necrotic RAMLs had undergone at least one distal embolization using microspheres. Due to the limited number of patients, the sub-group treated with microspheres alone could not be compared statistically to the sub-group embolized with coils alone. However, our results suggest a relationship between microspheres and tumor necrosis, even if it could not be demonstrated statistically.

Recent guidelines on the embolization of RAMLs in patients with TSC and uterine fibroids recommend that distal embolization using microspheres should be followed by proximal vessel occlusion with coils to achieve optimal efficacy [14,15,29].

In our patient population, microspheres (>500 μm) were used as the embolic agent for 17 of the 22 (74%) embolizations performed. In five of the six cases with necrotic RAMLs, embolization had been performed with microspheres of diameter >500 μm; in the remaining case, microspheres of 300–500 μm had been used. Pelage et al. [29] demonstrated that the risk of post-embolization uterine necrosis was greater when small microspheres (<500–600 μm) were used due to distal artery occlusion. This risk was higher for tumors sized >10 cm [30]. With regards to uterine fibroid embolization, Trillaud recommended using free-flow embolization with calibrated microspheres, in particular for tumors sized >10 cm [31].

In our study, the decision to perform arterial embolization for RAML was taken after discussion by a multidisciplinary team of specialists (urologists and radiologists).
is consistent with the management of other conditions that require arterial embolization [32,33].

The main limitation of this retrospective study is the low number of necrotic lesions. A greater number of necrotic cases would have allowed for discriminant statistical analysis based on the fat content or the embolic agents used.

However, our data suggest that necrosis occurs more frequently after the distal embolization with microspheres of large, high fat content RAMLS. Further investigation is required to confirm this hypothesis via multicenter studies including larger numbers of patients.

Conclusion

Tumor necrosis following RAML arterial embolization is an underestimated complication that can require surgical or percutaneous drainage. It seems to occur predominantly in large, high fat content (>50%) tumors treated by distal embolization with microspheres (associated or not with proximal embolization with coils).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

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