Polyvinyl alcohol and N-butyl cyanoacrylate for transarterial embolization of ruptured renal angiomyolipomas

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Abstract Objective: To evaluate using of polyvinyl alcohol particle and N-butyl cyanoacrylate (NBCA)/lipiodol mixture for selective embolization of eight patients with ruptured renal angiomyolipomas (AMLs).

Patients and methods: From January 2006 to December 2012, eight patients underwent angiography and embolization of renal angiomyolipoma-associated hemorrhage. The patients were 7 women and one man, 22–52 years old. Only 2 patients had the sporadic form of angiomyolipoma and the other 6 patients had the tuberous sclerosis form. Two patients presented with hematuria, while the other 6 patients presented with perinephric bleed. Three patients were treated urgently, while the other 5 patients were scheduled for embolization 1–3 days after admission. The technical and clinical success, complications, rebleeding and the need for surgical intervention were documented.

Results: Angiography showed aneurysmal dilatation in 7 patients (88%). Twenty-five feeding arteries were embolized. Primary technical success rate was 62.5% and the clinical success rate was 100%. No major complications or deaths occurred during or after the procedures. Mean hospitalization was 5 (range 3–12) days. Secondary technical success rate was 100%. No tumor growth on the follow up CT and the mean size reduction was 41%.

Conclusion: Selective arterial embolization with polyvinyl alcohol particles and N-butyl cyanoacrylate/lipiodol mixture is an effective and safe treatment for patients with ruptured renal AMLs.

1. Introduction

There are two types of angiomyolipomas (AMLs); the first is the more common sporadic type representing 80% of all AMLs, and the second type is the AML associated with tuberous sclerosis (TS) that represents the remaining 20% of AMLs (1,2). AML was described as the most common cause...
of perinephric hemorrhage (3) because it commonly ruptures into the perinephric space. Rarely, AMLs rupture into the renal collecting system causing hematuria. It was reported that 50–60% of AMLs measuring 4 cm or more bleed spontaneously (2), and that the larger the tumor, the greater is the risk of bleeding. So, it is generally agreed that patients with asymptomatic AML larger than 4 cm should be treated, as should those with symptomatic lesions of any size (4). The bleeding tendency originates from the abnormal aneurysmal tortuous blood vessels that constitute the angiogenic component of the tumor (5), therefore, angi embolization has become increasingly widespread for treatment of AML-associated bleeding. This study was performed to report our experience in treating 8 patients having AML associated with hemorrhage, with selective arterial embolization (SAE) using polyvinyl alcohol particles (PVA) and N-butyl cyanoacrylate (NBCA)/lipiodol mixture.

2. Patients and methods

Institutional review board approval was obtained for this retrospective study. From January 2006 to December 2012, eight patients were referred for angiography and embolization of renal AML-associated hemorrhage. The patients were 7 women and one man, 22–52 years old (mean age, 36 years). Only 2 patients had the sporadic form of AML and the other 6 patients had the TS form. Two patients presented with hematuria, while the other 6 (75%) patients presented with perinephric bleed. Of this later group, one patient presented with bilateral large AML and left perinephric bleed and underwent bilateral AMLs embolization in the same session. The patients were initially examined with ultrasound (US), then the presence of AMLs was confirmed by unenhanced and enhanced computed tomography (CT). We relied on observation of lipomatous density within the tumor to diagnose AML. Also the retroperitoneal hematoma was identified on both US and CT. Patients presented with hematuria, underwent cystourethroscopy to identify the bleeding side. The patients were treated initially with infusion of packed red blood cells for hemodynamic instability. SAE was indicated either to control severe hemorrhage from AML in hemodynamically unstable patients, or to prevent rebleeding in stable patients. Only three patients were treated urgently, at the same day, due to hemodynamic instability, while the other 5 patients were scheduled for embolization 1–3 days after admission. The technical success of the procedure was documented by postprocedural control angiogram. It was defined as the ability to perform total devascularization of the AML. The clinical success was documented by the ability of the SAE to stop bleeding based on disappearance of gross fresh hematuria, absence of enlarging perinephric hematoma on ultrasound examination, absence of recurrent need for erythrocyte administration, and absence of need for subsequent renal surgery to stop bleeding.

Embolization was performed under local anesthesia and through the common femoral artery. The procedure started with flush aortogram for evaluation of extrarenal arterial feeders to the tumor. Afterward, selective renal artery catheterization was performed using 5 French Cobra (C2), RDC or Simmonds (S1) angiographic catheters. The feeding vessels of the tumor were catheterized by microcatheter (2.4–2.8 French, Progreat, Terumo Co., Tokyo, Japan) introduced coaxially through the diagnostic catheter. The catheter tip was placed distal to the renal artery branches supplying normal parenchyma. Embolization was performed with polyvinyl alcohol particles (PVA) 150–250 and 300–500 μm, (Contour, Target, Boston Scientific) respectively, to block the tumor periphery. Larger proximal arteries and the pseudoaneurysms were embolized lastly by 20–25% NBCA/lipiodol mixture (Fig. 1). Antibiotic prophylaxis (cefoxime intravenous infusion (IVI) 1.5 g plus and metronidazole IVI 500 mg) was routinely given just before and continued 48 h after the procedure. Patients were routinely treated with nonsteroidal anti-inflammatory drugs (NSAID) during hospitalization.

Nephrectomy was performed for one patient, 5 weeks after embolization for radical treatment of the mass. The other 7 patients underwent outpatient follow-up examinations, urinalysis and estimation of serum creatinine level by a urologist every 3 months in the first year, and once a year thereafter for 12–40 months (mean, 24 ± 4 months). Unenhanced and enhanced CT was performed 3 months after embolization to detect remnants of the angiographic component of the AML. Re-embolization was considered if the first embolization was incomplete, or follow-up CT imaging showed residual vascularization of AMLs. In the second session, we used small sized PVA particles only for embolization, because most of the residual arteries were small sized. The second follow up CT was performed six months after total devascularization of the AML. Only 3 patients performed a third CT after 12–18 months.

3. Results

The tumor was bilateral in 6 patients (75%) who had TS, and unilateral in the other 2 patients with sporadic type of AML. Only the ruptured tumors were included in this work. The size of ruptured AMLs ranged from 5 to 18 cm measured in the largest diameter on CT obtained before angiography (Table 1). Angiography showed tortuous and stretched vessels in all the 8 ruptured AMLs and aneurysmal dilatation in 7 (88%). We found solitary aneurysm in 4 AMLs and 2 aneurysms were identified in the other 3 AMLs. The aneurysm size ranged from 1 to 3.5 cm. A single arterio-venous shunting was found in one patient. Two to four arteries were embolized in each ruptured AML (mean 2.6 arteries/tumor). Twenty-five feeding arteries were embolized, which consisted of 3 segmental, 8 proximal interlobar, 12 distal interlobar, and 2 renal capsular arteries. Complete immediate devascularization of the tumor vessels was achieved in 5 patients (62.5% primary technical success rate), while subtotal devascularization was done in the remaining 3 patients. The latter group was treated on emergency bases and we found involvement of multiple interlobar branches that made total embolization lengthy (in patients with bad general condition) and carries high risk of major renal ischemia.

No major complications or deaths occurred during or after the procedures. Signs of post-embolization syndrome were observed in 5 (62.5%) patients; including fever, pain, nausea and sometimes vomiting. All were treated conservatively with successful disappearance of these symptoms within 2–5 days. Non-targeted disappearance was documented in two patients due to backflow of the embolization particles, but no
significant changes of the renal functions were identified in the
follow up laboratory studies. None of our patients developed
recurrence of bleeding (clinical success rate 100%) or required
further emergency surgery to stop bleeding.

Mean hospitalization was 5 (range 3–12) days. A second
session of elective embolization was performed for 3 patients,
13–15 weeks after the first session, either due to subtotal devas-
cularization ($n=2$) of the AML on the postprocedural con-
trol angiogram, or enhancement of the angiographic
component of the AML on follow up CT ($n=1$). Total angio-
graphic devascularization was achieved in all patients (Sec-
ondary technical success rate 100%).

Follow-up CT for 7 patients after 3 months showed no
tumor growth, and the largest diameter of the tumors had
decreased 10–35% (mean reduction, 25%) after 3 months.
After 6 months of total devascularization, CT showed success-
ful devascularization of all AMLs with tumor length reduction
25–60% (mean reduction, 41%) (Table 1).

4. Discussion

Symptoms of AMLs uncommonly occur in lesions measuring
less than 4 cm in opposite to larger ones, of which 80–90%
are becoming symptomatic (6). We found that true in our
patients, as all of them had AMLs larger than 4 cm. The
TS-associated type represented 75% of all cases in our study
that adds confirmation of its more aggressive nature than the
sporadic tumor type (7). Two morbidities are responsible for
AMLs bleeding. The first is development of micro and macro-
aneurysms as the blood vessels within AMLs are abnormal
with no internal elastic lamina. These aneurysms may rupture
causing perinephric or retroperitoneal life-threatening hemor-
rhage. The presence of macroaneurysms in 88% (7/8) of the
examined ruptured AMLs supports the strong association
between aneurysm formation and bleeding, that was described
by Yamakado et al. in 2002 (8). Also, Rimon et al. (9) investi-
gated the correlation between symptoms and vascularity based
on digital subtraction angiography (DSA) and computerized
tomography (CT). They found that large AMLs with minimal
vascularity were less likely to bleed (9). The second uncommon
morbidity issue associated with renal AMLs is the invasion of
normal renal tissue and pelvi-caliceal system, leading to renal
failure (10) and hematuria which occurred in only two of our
patients (25%).

The available treatments for AMLs include; open surgery
(tumectomy, partial/total nephrectomy) (11–15), laparo-
sopic and robotic surgery (16,17), selective renal arterial embo-
lization (SAE) (18–24), radiofrequency ablation (25), and
laparoscopic cryoablation (26). Treatment of hemorrhagic
AML is a balance between the need to stop life-threatening
bleeding and to preserve as much functional renal parenchyma as possible. Surgical procedure such as nephron sparing surgery (NSS) eliminates the need for recurrent angiography and SAE, however it has an overall complication rate of 12% including 5% risk of urinary fistula (12). Also, the presence of retroperitoneal hematoma may complicate surgery, increases the likelihood of major reduction of renal parenchyma, and total nephrectomy is usually the end result. This makes surgery lose the advantage of preservation of the renal parenchyma, which is crucial in many cases such as previous renal insufficiency, a solitary kidney, autosomal dominant polycystic kidney disease, or other medical diseases. Chang et al. (27) studied 7 patients with ruptured angiomyolipomas who underwent urgent SAE within the first 24 h. Two patients underwent surgery because of persistent hematoma that ended by total nephrectomy due to adhesions and easy bleeding on touch. Furthermore, patients with TS complex, associated with large sized, centrally placed (extend to the hilum) and multiple angiomyolipomas have a limited role of NSS (28). The advantages of SAE include; less invasive, shorter hospital stay, negligible blood loss, and very low complication rate. The disadvantages include; non-eradication of the disease (mean length reduction after 6 months is 42%), and the need for repeated procedures. SAE is clearly beneficial in treating acute hemorrhage from AMLs, allowing hemodynamic stabilization of the patient and may obviate the need for subsequent surgery. We succeeded to stop bleeding in all of our patients (clinical success 100%) and the reported efficacy of SAE in achieving hemostasis is 77–100% after a single session of SAE (20–22,24,29). Total devascularization is not mandatory in the critical stage as we had 100% clinical success, despite the lower technical success of 62.5% for total devascularization. The interventionalist should start embolization by selection of the aneurysms-carrying arteries to get immediate hemostasis. If total devascularization is difficult, carries risk of inadvertent embolization, or needs long time in generally ill patient, subtotal devascularization is better and completion of the embolization could be performed 3 months thereafter simply and safely.

For SAE of AML, many embolizing materials were used successfully such as absolute ethanol with or without lipiodol (19,21,30), coils (5), PVA (18), or gelatin sponge (Gelfoam) (18). Also, embosphere (31), onyx (32), and amplatzer vascular plug (33) were used in case reports. Absolute ethanol ablation was found effective in AML embolization (34), causing complete obliteration of aneurysms and the entire arteriocapillary system. The disadvantage of the use of absolute ethanol ablation is the inability to visualize ethanol fluoroscopically causing fear of occlusion of non-target arteries by reflux. The balloon occlusion technique may reduce the possibility of non-targeted embolization, however, superselective catheterization of small renal arterial branches is technically difficult and may induce spasm (35), or occlusion of proximal non-targeted arterial branches. Furthermore, Zerhouni et al. (36) and Alder et al. (37) reported aneurysmal rupture during embolization, with forced alcohol injection that increases intravascular pressure and cause alcohol erosion of the aneurysm wall. Ethanol-iodized oil mixture has also been used in the embolization of AMLs (18,19). The iodized oil has been thought to act as an inert material, enhancing the embolic effect of the alcohol by producing more homogeneous distribution of the agent and increasing its contact time with tissue (35). The use of PVA particles in embolization of AML did not gain a consensus. It was reported that PVA particles do not penetrate the capillary level (34), and most large vessels containing PVA particles were incompletely occluded with particles embedded in the walls with increased risk of aneurysm rupture if PVA particles were used alone for AML embolization (38). Many interventionists have used coils for proximal arterial occlusion after PVA injection to maximize the embolic effect, by rapid cessation of flow in the targeted inflow artery (5). NBCA was used in the current study instead of coils to augment the effect of PVA and prevent recanalization. Despite the danger of catheter gluing, the risk of non-target embolization, and the need for higher experience, we have not witnessed any significant problem with this cheap embolic material. NBCA/lipiodol mixture provides total embolization of the proximal arteries and fills the irregular shaped aneurysmal dilatations, preventing recanalization or aneurysm re-rupture.

SAE is a minimally invasive procedure, but it is not devoid of complications. The most common complication is the postembolization syndrome reported in up to 85% of cases in previous studies (39,40), and in 62.5% (5/8) of the current study. Other rare complications after SAE such as abscess formation (41), pulmonary hypertension (42), lipiduria (43), liquid necrosis of the AML (44), moderate pleural effusion (19), and non-targeted embolization of renal tissue (23) have been reported in the literatures. Non-targeted embolization

Table 1 Summary of the clinical and angiographic data of the 8 patients.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/gender</th>
<th>Presentation</th>
<th>Embolized tumor length (cm)</th>
<th>Number of feeders</th>
<th>Presence of aneurysm</th>
<th>Degree of devascularization</th>
<th>Post-embolization results</th>
<th>Rebleeding</th>
<th>Complications</th>
<th>% Length reduction after 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/F</td>
<td>Hematuria</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>Subtotal</td>
<td>No</td>
<td>PES/NTE</td>
<td></td>
<td>(excised)</td>
</tr>
<tr>
<td>2</td>
<td>33/F</td>
<td>Perinephric H. 9</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>Subtotal</td>
<td>No</td>
<td>PES</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>41/M</td>
<td>Perinephric H. 18</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>Subtotal</td>
<td>No</td>
<td>PES</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>32/F</td>
<td>Hematuria</td>
<td>11</td>
<td>3</td>
<td>1</td>
<td>Total</td>
<td>No</td>
<td>NO</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>52/M</td>
<td>Perinephric H. 7</td>
<td>3</td>
<td>2</td>
<td>–</td>
<td>Total</td>
<td>No</td>
<td>NO</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>43/F</td>
<td>Perinephric H. 6</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Total</td>
<td>No</td>
<td>NO</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>37/F</td>
<td>Perinephric H. 10</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>Total</td>
<td>No</td>
<td>PES/NTE</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>22/F</td>
<td>Perinephric H. 5</td>
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<td>1</td>
<td>Total</td>
<td>No</td>
<td>PES</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

NTE, non-targeted embolization; PES, post-embolization syndrome; H, hemorrhage.
of small distal branches usually passes uneventfully in patients with normal renal function as we noted in two of our patients with multiple small feeders of the AML.

With conventional unenhanced and enhanced CT in the follow-up period after embolization, we found only 41% mean reduction in tumor size on CT performed 6 months after complete embolization, as have other investigators (4,19,44). There was no rebleeding in any of our patient, because we did not wait for clinical recurrence in patients underwent subtotal devascularization of the AMLs or showed enhanced angiographic component on the first follow up CT. We performed the second diagnostic angiography and embolization 13–15 weeks after the first session for total eradication of the angiographic component. Lee et al. (19) reported a re-embolization rate of 15.3% for treating AMLs with recurrent hemorrhage, or recurrence of symptoms within a mean follow-up time of 3 years. Kothary et al. (21) reported that after SAE no recurrences occurred in patients with sporadic AMLs, whereas 42.9% of TS-AMLs (9 of 21) showed recurrence. In Tso et al.'s (24) series, 1 patient required reembolization for treating a recurrence of symptomatic AML 16 months after the first treatment.

The most important limitation of our study is the small series of patients with relatively short follow-up, which made statistical analysis impossible. This is due to rarity of the lesions and missing of many patients after short time of their improvement.

Conclusion: SAE is effective and safe treatment for patients with ruptured renal AMLs. Embolization of the aneurysmal vessels should be the target in the acute stage with or without total devascularization of the AML. NBCA/lipiodol mixture could be used safely and effectively to augment the action of PVA particles and prevent proximal arterial recanalization.

Conflict of interest

None declared.

References