

Reduction of Postembolization Syndrome After Ablation of Renal Angiomyolipoma

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• Approximately 75% of patients with tuberous sclerosis complex develop renal angiomyolipomas. These hamartomatous lesions distort and damage renal parenchyma and can lead to hemorrhage. To reduce the risk of hemorrhage, transarterial embolization is used to necrose the angiomyolipoma while sparing normal renal tissue. Although an effective renal-sparing procedure, embolization most often is associated with an inflammatory response that causes significant fever and pain that can last for several days despite the use of acetaminophen. Reported cases show that 49 of 55 patients who underwent embolization developed this syndrome. The use of such nonsteroidal anti-inflammatory drugs as aspirin is contraindicated because of their adverse effects on platelet function. To reduce pain and fever associated with postembolization syndrome (PES), we changed our clinical management of patients postembolization to include a tapering dose of prednisone over a 2-week period. Nine patients underwent this pharmacological intervention, and one patient abstained. All patients were monitored for pain and fever. Only two patients treated with steroids developed fever, which was assuaged with acetaminophen, and no patient reported pain. The tapering dose of prednisone was well tolerated, and there were no postprocedure infections. The use of a short-term tapering dose of prednisone appeared to reduce PES compared with the reported literature and improved patient comfort.

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INDEX WORDS: Tuberous sclerosis complex (TSC); angiomyolipoma; postembolization syndrome (PES).

TUBEROUS SCLEROSIS complex (TSC) is an autosomal dominant inherited disease with a variable phenotype.¹ Renal manifestations of TSC are angiomyolipomas, cysts, and malignant tumors. Angiomyolipomas occur in 75% of children with renal lesions² and are described as hamartomatous lesions consisting of abnormal vessels, smooth muscle, and adipose tissue.³ These tumors demonstrate a clonal nature as well as a loss of heterozygosity, such that only the mutant allele can be identified at the TSC locus.^{4,8} These lesions may be discretely focal or coalesce into diffuse masses. Typically, angiomyolipomas are present in the young² and continue to grow during adulthood.⁹⁻¹¹ These lesions distort renal architecture and can compromise function. Renal failure is a long-term complication of TSC^{2,12} and the leading cause of death in adults.¹³ Although somewhat rare, angiomyolipo-

mas also can undergo malignant degeneration.¹⁴ Dysmorphic blood vessels in the angiomyolipoma can have microaneurysms¹⁵ or macroaneurysms.¹⁶ These aneurysms may rupture and hemorrhage, resulting in significant morbidity and, possibly, death.

Symptomatic angiomyolipomas have been treated by total nephrectomy, partial nephrectomy, enucleation, and embolization. Because of the loss of renal tissue, total nephrectomy is not optimal and is reserved for life-threatening conditions. Uncontrollable hemorrhage during partial nephrectomy and enucleation may necessitate total nephrectomy. Transarterial embolization, first used more than 20 years ago,¹⁷ has become the treatment of choice because of the renal-sparing nature of this procedure.¹⁸ Embolization can stop active bleeding or may be used prophylactically to treat large lesions believed to be at risk for hemorrhage.

An impediment to embolization is postembolization syndrome (PES). This syndrome causes pain and fever that can be severe.^{11,17,19-29} PES likely is caused by an inflammatory response to necrotic tissue after embolization. Burn et al³⁰ reported a patient with T₂-weighted magnetic resonance imaging findings compatible with liquefactive necrosis. Embolization of uterine fibroids³⁰ and whole kidneys³¹ in non-surgical candidates led to significant pain and fever. Inflammatory mediators in embolic and ischemic

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Received September 14, 2001; accepted in revised form November 30, 2001.

Supported in part by grants from the PKD Foundation and Tuberous Sclerosis Association (J.J.B.).

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0272-6386/02/3905-0007\$35.00/0

doi:10.1053/ajkd.2002.32770

diseases are being aggressively studied in atherosclerotic heart disease.^{32,33} Because of the possible immunologic cause of PES, steroids would be predicted to be a therapeutic benefit. Such therapy has been proposed to reduce PES³⁴ and has reduced pain after pulmonary resection³⁵ and interleukin-6 release after cardiopulmonary bypass.³⁶

Because of data in the literature and our own experience with patients with PES, we made a change in our clinical protocol for patients undergoing embolization for treatment of angiomyolipoma. With the new protocol, patients were administered prophylactic steroids after embolization. In this study, we retrospectively review our experience with this protocol.

PATIENTS AND METHODS

Patients

Ten patients, 1 of whom underwent two embolization procedures, were identified from more than 200 patients with TSC who attend a multisubspecialty clinic at Children's Hospital Medical Center (Cincinnati, OH). Two patients were identified by symptomatic lesional hemorrhage, and 7 patients were identified by angiomyolipoma lesions greater than 4 cm. One additional patient also was identified and underwent angiography without embolization. Two patients had single kidneys.

Informed consent and institutional review board approval were both sought and obtained for this work.

Angiography and Embolization

Indications for diagnostic angiography and embolization included acute hemorrhage or potentially prophylactic embolization of an angiomyolipoma greater than 4 cm. Procedures were performed under general anesthesia. Through a common femoral artery, puncture and placement of an arterial sheath, an aortogram, and bilateral (when both kidneys were present) selective renal arteriograms were performed. Angiographic criteria used to proceed to embolization included the presence of abnormal severely tortuous arterial structures or microaneurysms and/or macroaneurysms within the angiomyolipoma. Microcatheters were used to superselect arterial branches supplying the angiomyolipoma. These branches were embolized using a combination of polyvinyl alcohol particles (250 to 350 μ m) and embolization coils. In an effort to preserve as much normal renal parenchyma as possible, arteriograms were performed after each stage of embolization to determine the completeness of the embolization and identify other arteries that also might require embolization.

Postembolization Anti-Inflammatory Therapy

Before embolization, patients were administered the first dose of prophylactic first-generation cephalosporin and an intravenous dose of 250 mg/m² of methylprednisolone (maxi-

mum dose, 260 mg). Patients were administered four doses of antibiotics, with subsequent oral dosing. Beginning on the first postoperative day, patients were administered 2 mg/kg of prednisone in three divided doses per day for 2 days, with a maximum dose of 60 mg/d. Every 2 days, the dose was tapered to finish approximately 14 days after embolization, except for patients 1 and 3a, in whom doses were tapered more aggressively over 7 days to see whether the steroid taper could be more rapid. Patient 10 was not administered steroid therapy. For the first day after embolization, patients also were administered acetaminophen every 6 hours orally if needed.

Follow-Up

Patients were monitored for fever greater than 100.5°F and flank or abdominal pain during and after the 2-week course of steroids. Response to therapy was determined by a decrease in angiomyolipoma size shown on computed tomographic scan 2 to 3 months after the procedure. Serum creatinine levels, a measure of renal function, were determined before and approximately 1 month after embolization for all patients.

Literature Review

The published literature was searched for citations addressing PES and embolization of renal angiomyolipomas. The incidence of PES was calculated from the identified studies.

RESULTS

Patients and Angiomyolipomas

All patients met diagnostic criteria for TSC and were postadolescent (mean age, 26.6 \pm 7.5 years).^{1,37} Ten patients underwent angiography (Table 1). One patient was studied twice (Table 1; patient 3). Of these studied patients, only one patient (no. 4) did not meet embolization criteria. The other nine patients (patients 1 to 3 and 5 to 10) underwent embolization therapy. Patient 3 underwent two separate embolization procedures at different times on a single kidney, one of an upper-pole lesion and the other of a lower-pole lesion. Two patients presented because of hemorrhage (patients 3a and 8), whereas the remaining patients were studied and underwent embolization prophylactically based on lesion size.

Before embolization, mean angiomyolipoma size was 10 \pm 6.5 cm, not statistically different from that found in the literature.^{18,23,27} All angiomyolipomas underwent marked reductions in size (>2-cm reduction, often with a significant necrotic central portion), except for patient 5. This likely is because this patient's lesion was predominantly lipoma, and failure of size reduction for such adipose-predominant lesions previ-

Table 1. Angiomyolipoma Characteristics and Presence of PES in Children's Hospital Medical Center Patients

Patient No.	Location	Maximum Size of AML (cm)	Sex	Stay Length (d)	PES
1*	Right upper	9	M	2	+
2	Left lower	8	F	2	-
3a*	Right upper	16	F	10	+
3b	Right lower	9	F	2	-
4	Bilateral	Perinephric	F	2	-
5	Right lower	9	F	1	-
6	Left lower	7.2	M	1	-
7	Upper left	4.1	F	1	-
8	Left upper	25	M	1	-
9	Right upper	5	F	1	-
10*	Right upper	8	F	9	+

NOTE. PES for patient 1 consisted of a fever to 101.5°F, for which a single dose of acetaminophen was required 2 days after the procedure. Patients 3a and 10 had several days of fever greater than 101°F and flank pain.

Abbreviation: AML, angiomyolipoma.

*The patient did not receive the recommended dose and duration of prednisone therapy.

ously has been reported.²⁷ Figure 1 shows typical computed tomographic and angiographic appearances of an angiomyolipoma before, during, and after therapy.

Vascular Abnormalities

Because symptoms, including hemorrhage, have been associated with angiomyolipoma size, we studied patients angiographically to assess the risk for bleeding. All angiomyolipomas on our study, except that of patient 4, contained tortuous blood vessels, and seven angiomyolipomas contained aneurysms. We also noted that in patient 3, aneurysms developed over a 6-month period.

PES

The incidence of PES among the 55 treated patients with angiomyolipomas reported in the literature is 89% (Table 2). This rate of PES is similar to rates seen after embolization of other tissues.³⁸ The use of prednisone significantly reduced the rate of this complication. Only 3 of our 11 embolization patients had fever or pain, and these procedures were performed earlier in our experience and prednisone taper was over the course of a week. Physiological data, such as heart rate and blood pressure, were used to

corroborate the parental rating of the patient's pain in our four nonverbal patients. We screened patients for such steroid side effects as hyperglycemia, abdominal pain consistent with gastritis or pancreatitis, and blood pressure elevations, but failed to find these complications.

DISCUSSION

The risk for hemorrhage from angiomyolipomas is unknown. Published series suggest that hemorrhage occurs in half the patients and is related to the size of the lesion.^{39,40} In reviewing 178 patients in the published literature who had angiomyolipomas of 4 cm or greater, Oesterling et al³⁹ reported that 51% of these patients had a lesion hemorrhage. Because of the nature of publications, this result may not reflect the incidence in the population of patients with tuberous sclerosis. Furthermore, some series showed that smaller lesions also can hemorrhage.¹⁸ We hypothesize that vascular abnormalities, such as dysplastic arteries or aneurysms, contribute to the risk for hemorrhage.

Interventions to reduce the risk for hemorrhage have included open surgical and transcatheter radiological methods. Selective embolization has become the favored renal-sparing therapy for these lesions.⁴⁰ PES is a frequent complication of this therapy and much more common than infection in reported cases. The morbidity of PES led us to modify our therapy. Because we found such a dramatic improvement in patient tolerance, we chose to compare our patients with those previously reported instead of using a control group that underwent embolization without the use of steroid therapy. Using the literature as a control group is justified because lesion sizes in those reports were statistically similar, and the rate of the syndrome is similar for different tissues.³⁸ In our series, the use of steroid anti-inflammatory therapy reduced the adverse consequences of embolization therapy for angiomyolipomas associated with TSC. Additional studies may show that steroid therapy improves the postoperative course of other transarterial embolization procedures.

The use of steroid therapy to reduce swelling has been suggested for the postoperative management of embolized arteriovenous malformations³⁴ and has been shown to reduce pain associated with thoracic surgery³⁵ and reperfusion injury after car-

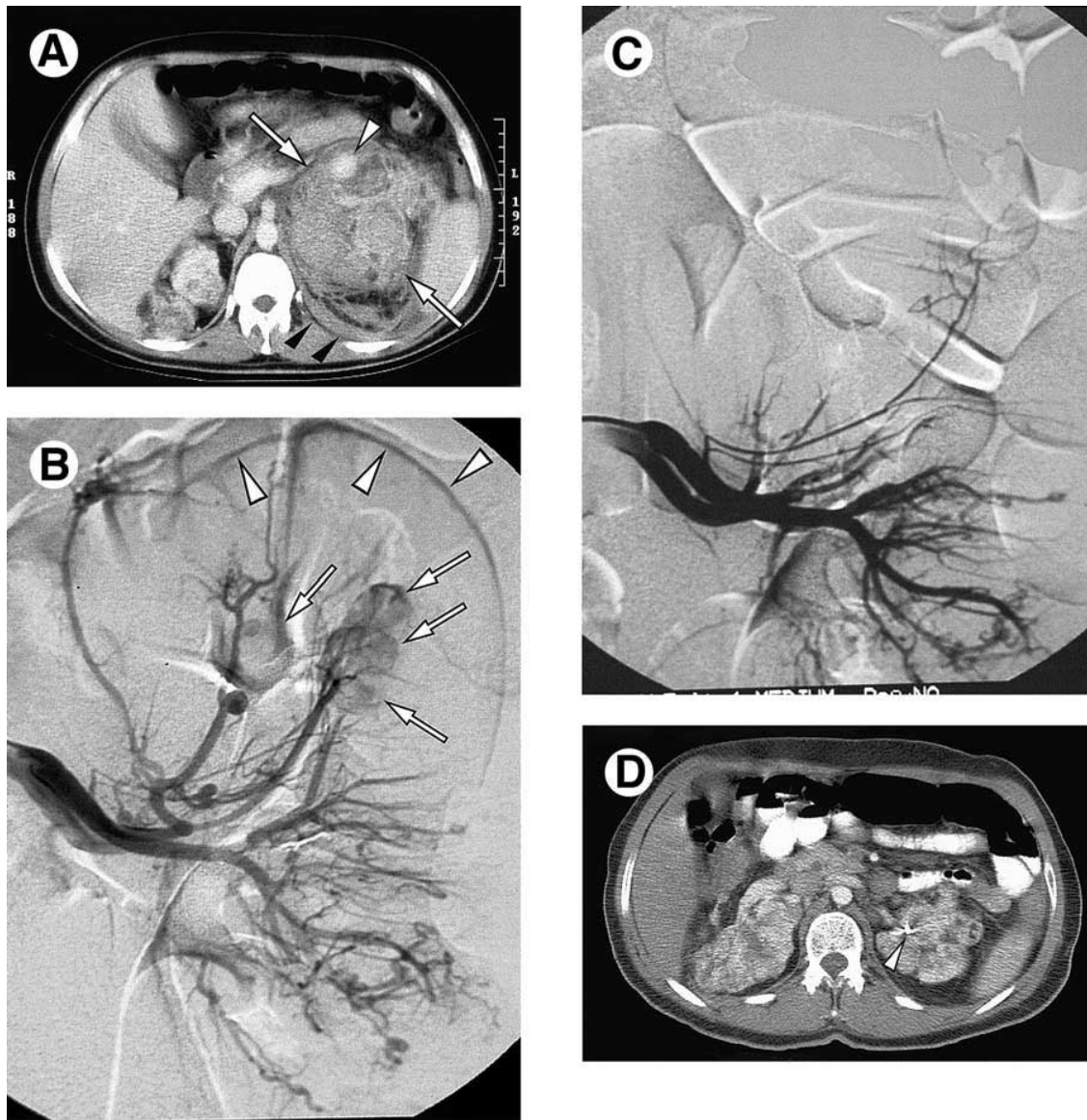


Fig 1. Angiomyelolipoma with spontaneous hemorrhage in a 26-year-old man with tuberous sclerosis. (A) Computed tomography shows areas of low attenuation within the kidneys bilaterally (arrows on the left), consistent with angiomyolipomas. Note abnormal soft tissue within the left perirenal space (black arrowheads), consistent with hemorrhage. Hemorrhage displaces the kidney anteriorly. An aneurysm is visible within the lesion (white arrowhead). (B) Arteriogram of the lower-pole branch of the left renal artery shows multiple areas of abnormal tortuous blood vessels and multiple small aneurysms (arrows). Embolization was performed of this region. Note displacement of capsular artery branches (arrowheads) by angiomyolipoma. (C) Arteriogram of vessels shown in B after embolization shows the cessation of blood flow to the angiomyolipoma. (D) Follow-up computed tomography several months later shows marked reduction in the size of the angiomyolipoma, good preservation of renal parenchyma, and the coil location (white arrowhead).

diopulmonary bypass.³⁶ Steroid therapy is used for immune modulation of autoimmune disorders and organ transplantation. With the use of such a powerful agent comes the risk for infection. Prophylactic

use of antibiotics in our patients was an attempt to reduce the risk for infection. Further investigation into the need for prophylactic antimicrobial therapy and better methods to screen for vascular abnormali-

Table 2. Reported PES in the Literature

Reference	No. of Patients	No. with PES
Yanai et al ¹⁹	1	1
Edelman et al ²⁰	1	1
Moorhead et al ¹⁷	1	1
Sanchez et al ²¹	1	1
van Baal et al ²²	4	4
Kessler et al ²³	7	7
Kennelly et al ¹¹	5	5
Soulen et al ²⁴	5	5
Hamlin et al ²⁵	5	5
Mourikis et al ²⁶	5	2
Lee et al ²⁷	15	12
Uchino et al ²⁸	1	1
Kehagias et al ²⁹	4	4
Total	55	49

NOTE. Not all articles discussing experience with embolization syndrome report PES; therefore, only articles that discuss this outcome are presented. Embolization protocols were variable.

ties in angiomyolipomas will aid greatly in the care of patients with TSC.

ACKNOWLEDGMENT

The authors thank Dr David Franz and the staff at the Tuberous Sclerosis Clinic at Children's Hospital Medical Center.

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