

# Renal Cell Carcinoma 9 Years After Contralateral Resection for Angiomyolipoma in a Patient Without Tuberous Sclerosis

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**T**he diagnosis of renal cell carcinoma versus renal angiomyolipoma can be difficult. Renal cell carcinoma is the most solid renal tumor, and angiomyolipoma is an uncommon tumor of the kidney occurring mostly in patients with tuberous sclerosis. In 1862, von Recklinghausen<sup>1-3</sup> first described the cerebral lesions of tuberous sclerosis. Bourneville<sup>4</sup> later recognized these lesions as part of a clinical syndrome associated with mental retardation, epilepsy, and adenoma sebaceum. In 1911, Fischer<sup>5</sup> described hamartomatous renal lesions in conjunction with tuberous sclerosis, and, in 1951, Morgan et al<sup>6</sup> first used the term *angiomyolipoma*.<sup>1,7</sup> Further investigation has revealed that tuberous sclerosis is a rare autosomal disorder that displays incomplete penetrance; 50% of the cases of renal angiomyolipoma manifest in patients with tuberous sclerosis and 40% to 80% of patients with tuberous sclerosis exhibit angiomyolipoma.<sup>8-11</sup> Whether angiomyolipoma is a *de novo* neoplasm, an anomaly of embryonic tissue, or a genetically inherited defect is not clear.<sup>12-14</sup>

Bilateral renal angiomyolipomas, although uncommon, are often demonstrated in patients with tuberous sclerosis.<sup>15,16</sup> In addition, a rare association between angiomyolipoma and renal cell carcinoma has been documented; in a review of ten patients with coincidental angiomyolipoma and renal cell carcinoma, 50% exhibited tuberous sclerosis.<sup>17</sup> Consequently, the presence of angiomyolipoma with renal cell carcinoma without tuberous sclerosis represents an exceedingly rare event.

This article discusses a case of renal cell carcinoma occurring in a patient 9 years after angiomyolipoma and right nephrectomy without tuberous sclerosis. In addition, a review of the literature is presented.

## CASE PRESENTATION

A 39-year-old man presents to the emergency department with left-sided abdominal pain of 1 month's duration and a palpable upper left quadrant mass without hematuria. The patient's medical history is significant for angiomyolipoma (**Figure 1**) and right nephrectomy 9 years prior to the current presentation.

## Laboratory Studies, Diagnosis, and Treatment

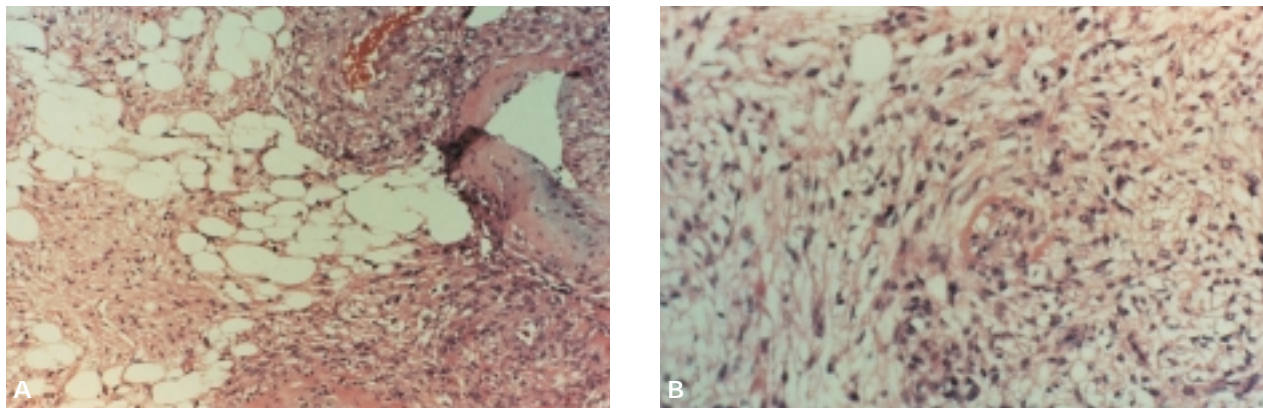
Following hospital admission, a complete blood count and renal profile are within normal limits. Computed tomography (CT) of the abdomen demonstrates a 10-cm mass without lymphadenopathy at the lower pole of the left kidney (**Figure 2**) and contrast medium leaking from the left kidney. Recurrent angiomyolipoma is diagnosed. Renal arteriography reveals a large space-occupying lesion in the lower pole of the left kidney with a moderate amount of neovascularity (**Figure 3**). The branch of the left renal artery that is supplying the lesion in the kidney's lower pole is selectively embolized with a stainless steel coil. After the procedure, a significant decrease in blood supply to the mass is evident (**Figure 4**). The patient is discharged home the following day.

## Additional Presentation, Surgical Biopsy, and Outcome

The patient returns to the emergency department 8 days after embolization with complaints of progressive, unremitting left abdominal and groin pain. The

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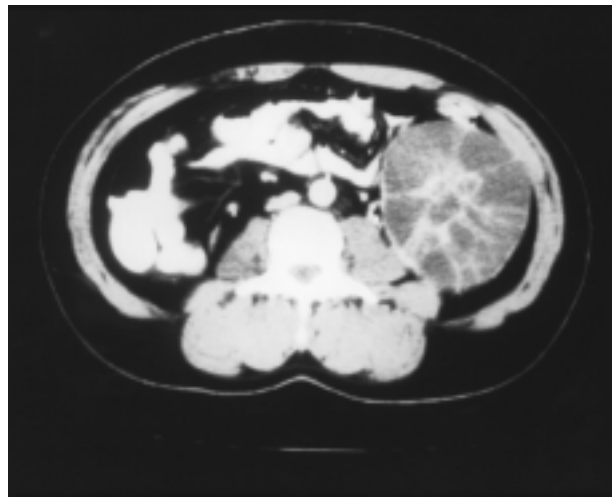


**Figure 1.** Histopathologic view of the angiomyolipoma resected 9 years before the patient's current presentation. A) Low-power magnification demonstrates mature fat cells, as well as atypical dysplastic blood vessels with thickened walls, and smooth muscle sheets streaming into the fat regions. B) High-power magnification demonstrates renal angiomyolipoma.

patient undergoes a left partial nephrectomy with removal of the 10-cm mass. Histopathologic examination of the mass reveals a multiloculated cystic structure with multiple septa composed of renal clear cell carcinoma (**Figure 5**). The tumor is more than 2.5 cm in its greatest dimension, the regional nodes cannot be assessed, and no distant metastasis is evident; the tumor is staged as T2NXM0. The patient's postoperative course is uneventful and he is discharged home.

#### DISCUSSION

Angiomyolipomas represent 1% to 2% of all renal tumors and are classified into two clinical subtypes.<sup>15</sup> The first subtype of angiomyolipoma is associated with tuberous sclerosis and is normally asymptomatic.<sup>1,12,15,18</sup> Lesions of the first subtype are usually small, multifocal, bilateral, and most often found at autopsy.<sup>1,12,15,18,19</sup> The second subtype of angiomyolipoma is independent of tuberous sclerosis. Lesions of the second subtype are commonly unilateral, solitary, larger than lesions of the first subtype, and most frequently diagnosed in women age 40 to 70 years.<sup>1,12,15,16,20-22</sup> In addition, the second subtype of angiomyolipoma is usually symptomatic on presentation and is associated with a tender flank mass (87% of cases), palpable mass (40% of cases), pain secondary to intrarenal or retroperitoneal hemorrhage (47% of cases), and hematuria (40% of cases).<sup>2,4,15,23,24</sup> Similar to angiomyolipomas, renal cell carcinoma in patients with tuberous sclerosis usually presents as multifocal lesions in both kidneys simultaneously. In patients without tuberous sclerosis, renal cell carcinoma manifests as a unilateral, solitary lesion similar to angiomyolipoma.<sup>17</sup> Therefore, diagnosis of malignant versus benign renal disease can be difficult.



**Figure 2.** Computed tomography demonstrates a 10-cm septate mass in the lower pole of the left kidney without lymphadenopathy.

There are 10 reported cases of angiomyolipoma associated with unilateral or bilateral renal cell carcinoma in patients with or without tuberous sclerosis.<sup>25</sup> In addition, one case of angiomyolipoma developed 7 years after resection of a renal cell carcinoma,<sup>26</sup> and one case of death in a patient with concurrent tuberous sclerosis, renal angiomyolipoma, and renal cell carcinoma was reported.<sup>27</sup> Whether this patient's death was secondary to the renal cell carcinoma or the tuberous sclerosis is unknown.<sup>9,25,28</sup>

In the patient in this case study, the solitary renal lesion was predicted to be renal cell carcinoma based on the incidence rate (85%) and nature of this disease.



**Figure 3.** Renal arteriography reveals a large space-occupying lesion in the lower pole of the left kidney with a moderate amount of neovascularity.



**Figure 4.** Renal arteriography shows a significant decrease in blood supply to the mass after a lower pole branch of the left renal artery supplying this lesion is selectively embolized.

Considering the history of angiomyolipoma resection 9 years prior to the patient's presentation, however, a diagnosis of recurrent hamartomatous disease was made.<sup>29</sup>

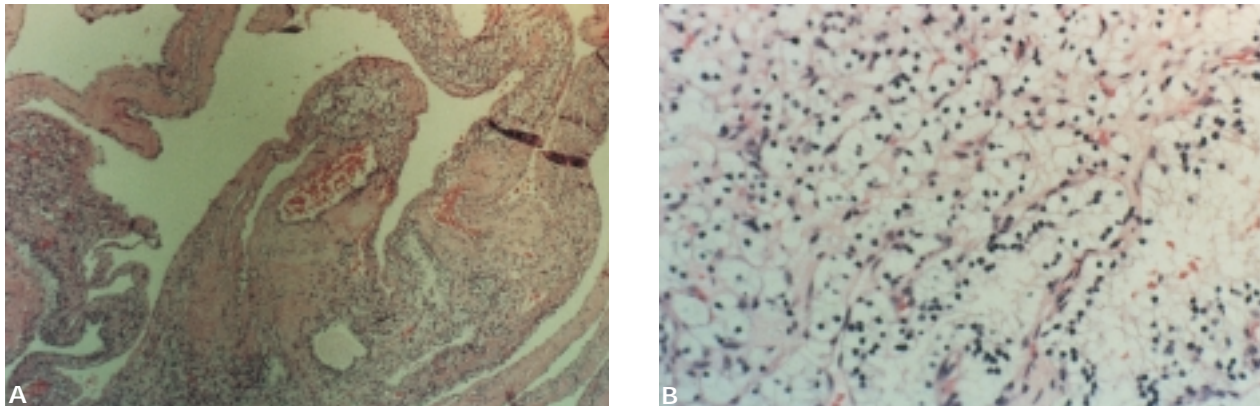
#### Diagnosis

**Radiography and pyelography.** Standard radiography can be used to identify renal cell carcinoma if the lesion contains calcifications. A tumor with calcifications should be considered malignant until proven otherwise, and most angiomyolipomas rarely contain calcifications.<sup>25,30</sup> Intravenous pyelography has also been used to distinguish between angiomyolipomas and renal cell carcinoma. However, radiography and pyelography are limited because these studies only demonstrate renal parenchyma and collecting system or ureter deviation. Intravenous pyelography may also confuse the diagnosis of angiomyolipoma with polycystic kidney disease, especially if the disease is bilateral and multicentric within the kidneys.<sup>10,18,31</sup>

**Ultrasonography and computed tomography.** Angiomyolipomas are most often diagnosed by ultrasonography or CT.<sup>32</sup> Ultrasound demonstrates a highly echogenic pattern and defines renal cortex masses well; both findings are indicative of angiomyolipoma. The diagnostic echogenic patterns are secondary to high fat content and multiple fat-to-nonfat interfaces, which

are virtually diagnostic because fat is not found in the renal parenchyma.<sup>9,24,31,33,34</sup> CT can also distinguish between the multiple fat-to-nonfat interfaces. The negative attenuation values derived from the CT scans correspond to fat content within the angiomyolipoma and virtually exclude the diagnosis of renal cell carcinoma.<sup>9,31,34</sup> In the patient in this case study, CT scans (Figure 2) demonstrate the fat-to-nonfat interfaces indicative of angiomyolipoma and confirm the presumed clinical diagnosis of recurrent angiomyolipoma.

**Angiography.** Once considered to be pathognomonic for the diagnosis of angiomyolipoma, angiographic findings are now considered unreliable.<sup>35,36</sup> The presence of benign neovascularity with terminal aneurysms in the lobar and interlobular arteries, as demonstrated in the patient in this case study (Figure 3), as well as whorled "onion peel" with venous phase, "corkscrewing" arteries, and absent arteriovenous shunts are suggestive of angiomyolipoma.<sup>1,7,31</sup> However, many patients with renal angiomyolipoma do not demonstrate these findings.<sup>35-37</sup> In patients with a unilateral highly vascularized lesion confirmed by angiography, some investigators believe that a renal biopsy should be considered.<sup>2,31</sup> Other investigators conclude that angiography does not provide the structural and anatomic detail to differentiate between angiomyolipoma and renal cell carcinoma.<sup>2,25</sup> Currently, angiography is used to provide means for embolization



**Figure 5.** Histopathologic examination reveals renal clear cell carcinoma. A) Low-power magnification demonstrates a multiloculated cystic structure with multiple septa composed of renal clear cell carcinoma. B) High-power magnification demonstrates renal clear cell carcinoma.

in order to either treat active hemorrhage or symptomatic lesions.<sup>17,38</sup> The tendency for hemorrhage is a result of the hypervascularity of these hamartomas, which may require emergent exploration and possible nephrectomy if embolization is not successful.<sup>7,15,31,39,40</sup>

#### Treatment

Surgical intervention necessary to maximize renal function includes enucleation and partial nephrectomy. Total nephrectomy should be reserved for uncontrollable hemorrhage after failed attempts at embolization or if renal cell carcinoma is a possibility.<sup>7,15,31,39,40</sup>

In 1986, Oesterling et al<sup>38</sup> outlined surgical management of renal angiomyolipomas. According to this study, lesion size and symptomatology determined the course of management. Asymptomatic lesions did not require surgical intervention, regardless of their size. However, symptomatic lesions greater than 4 cm usually required surgery because of a greater risk of spontaneous rupture and associated hemorrhage (**Table 1**).

In the patient in this case study, preoperative embolization did not ameliorate the pain and discomfort caused by the mass and, therefore, left partial nephrectomy was performed. Histopathologic analysis of the resected specimen led to the diagnosis of renal cell carcinoma (Figure 5). Subsequently, the patient's previous diagnosis of angiomyolipoma was questioned. Analysis of the resected specimen 9 years prior to the current presentation demonstrated the characteristic histopathologic appearance of a renal angiomyolipoma. The composition of the hamartoma and predominant cell type was primarily mature fat cells, atypical dysplastic blood vessels with thickened walls, and smooth muscle sheets streaming into the fat regions—classic pathologic findings for

renal angiomyolipomas (Figure 1).<sup>9,12,15,18,23,41</sup> Whereas renal cell carcinoma is a malignancy with the potential to metastasize, angiomyolipoma is not considered a malignant tumor although it may minimally extend into the perinephric tissues.<sup>12,35,42,43</sup>

#### Genetic Factors

Molecular studies of patients with renal cell carcinoma and angiomyolipoma have suggested a possible genetic or hereditary link between these two entities.<sup>44,45</sup> Cohen et al<sup>46</sup> originally described a family in which eight out of 10 family members demonstrated an association between angiomyolipoma and renal cell carcinoma. Genotypic analysis revealed a constitutional reciprocal translocation between chromosomes 3 and 8 [t(3;8)/(p14;q24)].<sup>46,47</sup> In addition, genetic anomalies in patients with renal cell carcinoma have been demonstrated on chromosomes 3 and 11.<sup>29</sup> A recent study identified a family with multigenerational tuberous sclerosis having a mutant tuberous sclerosis-causing gene on chromosome 9, termed *TSC1*.<sup>14</sup> This report suggests that constitutional mutations at the *TSC1* loci may predispose patients to renal cell carcinoma, as originally described by Cohen.<sup>14</sup>

In the patient in this case study, the previous angiomyolipoma may have predisposed the patient to the subsequent development of renal cell carcinoma, even 9 years later. Whether patients with or without tuberous sclerosis, who manifest angiomyolipoma, are predisposed to developing renal cell carcinoma as a result of a specific genetic mutation still needs to be determined. Therefore, any renal angiomyolipoma should be suspected as a premalignant lesion for renal cell carcinoma. A thorough work-up of the renal mass must ensue without the prior bias of the patient's medical history.

**Table 1.** Surgical Management of Renal Angiomyolipomas

Symptomatology	Lesion size, cm	Intervention
Asymptomatic	< 4	Ultrasound or computed tomography scan every year
Asymptomatic	> 4	Ultrasound or computed tomography scan every 6 months
Symptomatic	< 4	Angiogram with embolization and/or conservative surgical intervention If symptoms resolve, then ultrasound or computed tomography scan every 6 months
Symptomatic	> 4	Angiogram with embolization and/or conservative surgical intervention (enucleation/partial nephrectomy)

Data from Oesterling JE, Fishman EK, Goldman SM, Marshall FF: The management of renal angiomyolipoma. *J Urol* 1986;135:1121-1124.

**SUMMARY**

The unusual combination of renal cell carcinoma 9 years after removal of a contralateral angiomyolipoma is extremely rare. Although renal angiomyolipoma is uncommon, patients with renal angiomyolipoma may be at a higher risk for developing renal cell carcinoma. Further molecular studies are needed to determine what predisposes a patient with renal angiomyolipoma to renal cell carcinoma. In addition, the patient's medical history should not bias the physician's thorough work-up of a renal mass. **HP**

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