original article

The impact of renal angiomyolipoma on estimated glomerular filtration rate in patients with tuberous sclerosis complex

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Ann Saudi Med 2016; 36(5): 356-363

DOI: 10.5144/0256-4947.2016.356

BACKGROUND: There is a growing concern that renal impairment may develop in patients with renal angiomyolipomas (AMLs) associated with tuberous sclerosis complex (TSC) as a consequence of the disease itself and/or the interventions to mitigate the risk of hemorrhage.
OBJECTIVE: To assess the estimated glomerular filtration rate (eGFR) in patients with bilateral renal AMLs and the impact of tumor burden and intervention on renal function.
DESIGN: Retrospective study.
SETTING: Urology department of a tertiary care hospital.
PATIENTS AND METHODS: All adult patients (≥18 years of age) with TSC-associated renal AMLs seen from October 1998 to June 2015. We included only patients with bilateral tumors or solitary kidneys at the last follow-up.
MAIN OUTCOME MEASURES: The eGFR, renal volume, and number and type of interventions.
RESULTS: We identified 12 patients (median age 27.6, interquartile range 23.7-39.9 years), a median follow-up period of 1266 days (33-3133), and a median renal size of 454.7 mL (interquartile range 344.7-1016.9 on the right side; 558.1 mL, interquartile range 253.7-1001.4 on the left). In 11 (91.7%) patients, the eGFR was >60 mL/min/1.77 m^2. Six patients had three total nephrectomies, one had a contralateral partial nephrectomy, and seven had selective arterial embolizations. Intervention was associated with a significantly reduced eGFR. The renal size did not correlate with the eGFR.
CONCLUSIONS: TSC-associated renal AMLs may attain a large size but normal renal function is maintained in 92% of patients. Interventions to mitigate the risk of hemorrhage are associated with decreased renal function.
LIMITATIONS: The renal size was used as a surrogate for tumor size. Other limitations were the limited number of patients and lack of split renal function testing.

Angiomyolipomas (AMLs) are benign fat-containing tumors that affect the kidneys. AMLs associated with the tuberous sclerosis complex (TSC) are often larger, usually bilateral, and grow more rapidly than AMLs in sporadic cases.[1,2] The greatest risk for patients with large lesions is life-threatening retroperitoneal hemorrhage. In a pooled analysis of renal AML cases, 44% of patients with TSC-associated AMLs presented with hemorrhages.[1] In contemporary series, most patients required interventions to control symptoms of hemorrhage, including total or partial nephrectomy in 58% and embolization in 42%.[3] Although prophylactic treatment to prevent hemorrhage and intervention to treat active bleeding are effective and safe,[4] preservation of renal function emerges as an important target for novel therapeutic approaches.[5] There is a growing concern that TSC-associated renal AMLs may cause renal impairment and failure.[5-8] Although renal diseases are reported as the leading cause of death in TSC patients, the exact pattern by which the deterioration of renal function contributes to mortality and the underlying risk factors are not known.[9] Factors that may affect the glomerular filtration rate (GFR) in those patients include tumor burden, as well as the nature and number

of interventions. Despite these concerns, we observed that some of our patients maintain a normal renal function in the presence of huge bilateral AMLs filling the entire abdomen. We conducted this study to identify how renal function is affected in TSC patients with large bilateral renal AMLs and the factors that may affect the estimated GFR (eGFR) in our tertiary care hospital.

PATIENTS AND METHODS

We conducted a retrospective study of all patients with TSC-associated renal AMLs who were referred to the urology department from October 1998 to June 2015. We included only those patients who met the clinical diagnostic criteria of TSC.[10] Data were collected from paper and electronic records and included age, sex, weight, height, serum creatinine levels, and type and number of interventions. We excluded pediatric patients <18 years of age at the last follow-up and patients with a normal contralateral kidney or with a solitary lesion less than 4 cm in diameter. The serum creatinine level was determined using the Jaffe Reaction Method (Roche Diagnostics, Basel, Switzerland). The eGFR was calculated using three equations for adult patients: the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault (CockG) equations. The Schwartz equation was used for one pediatric patient at initial presentation.[11-14] Renal size was calculated by using length, width, and depth from computed tomography (CT) or magnetic resonance images (MRI) by using the ellipsoid formula. Renal volume was independently measured by 3-dimensional (3D) reconstruction of the same images using General Electric Advantage Windows 4.6 Volume software (GE Healthcare, Little Chalfont, United Kingdom). The kidney volume was measured through contiguous slices using free-hand outlining of the kidney. We compared data for patients who received any intervention to stop bleeding with those who did not need any intervention. We compared data for patients at their initial visit and last follow-up. We used the t test to compare continuous data and the chi-square or Fisher exact test (1-sided) for categorical data. Missing data were excluded from the analysis. We considered $P<.05$ significant. We used IBM SPSS statistics 20 software (IBM Corporation, Armonk, New York, United States) for statistical analysis.

RESULTS

We excluded two adult patients because of contralateral kidneys with solitary lesions that had the largest diameter of <4 cm. We evaluated 12 eligible patients; all had bilateral renal AMLs and 9 of them were females. All patients had at least two major criteria for the clinical diagnosis of TSC (**Table 1**). At the last follow-up , the median 3D renal volume for female patients for the right side was 492.6 mL (232.7-1933.8; standard deviation [SD] 598.1, n=8) and for the left side, 638.3 mL (166.6-2403; SD 880.1, n=7) (**Table 2**). For the three male patients, the right median renal volume was 450.8 mL (259.7-1016.9) and the left, 510 mL (223.5-606.2). The patients had a median eGFR >60 mL/min/1.77 m^2. There was a significant correlation between the GFR determined by using the three different methods: eGFR-MDRD correlated with eGFR-CKD-EPI (r=0.843, P=.001) and eGFR-CockG (r=0.632, P=.028), while eGFR-CKD-EPI correlated significantly with eGFR-CockG (r=0.76, P=.004). At the last follow-up, nine patients (75%) had an eGFR >90 mL/min/1.77 m^2. Two patients (16.7%) had an eGFR 60-90 mL/min/1.77 m^2 after two left total nephrectomies, one right partial nephrectomy, and two embolizations to control bleeding. One patient (8.3%) had an eGFR <60 mL/min/1.77 m^2 after left total nephrectomy and embolization. The volume of the kidney as determined by the ellipsoid formula correlated significantly with the 3D reconstructed volume (r=0.972, P<.001). There was no significant correlation between the total renal volume and creatinine level or GFR (**Table 3**).

Six patients (50%) (five females and one male) received 11 interventions to stop bleeding during follow-up. There was no difference between sexes in exposure to interventions (P=.5). The patients had seven selective arterial embolizations, three had a total nephrectomy, and one had a partial nephrectomy. The eGFR was significantly lower for patients who un-

Table 1. Criteria for clinical diagnosis of tuberous sclerosis complex.

Criteria	n
Major	
Bilateral renal AML	12
Subependymal nodules	11
Facial angiofibroma	10
Cortical dysplasia	2
Lymphangioleiomyomatosis	1
Subependymal giant cell astrocytoma	2
Minor	
Liver hamartoma	5
Retinal patch	1

derwent an intervention compared with that for those who did not receive any intervention (**Table 4**). Renal volume data at the initial visit and last follow-up were available for eight patients. There was no difference between baseline and last follow-up renal volume, creatinine level, or eGFR (**Table 5**).

DISCUSSION

AML tumor burden and renal volume determination

We determined renal volume as an indicator of AML burden rather than measuring individual lesions, because in many cases it was difficult to distinguish between the numerous AML lesions that filled the kidneys and normal tissues (**Figure 1A, B**). The complexity of renal tumor burden significantly impairs individual tumor size measurement. A study of renal tumor burden by CT semiautomated volume determination of selected tumors showed high inter-observer and intra-observer variability that was even larger for the ellipsoid formula calculation.[15] We determined the renal volume by two different methods, and two independent teams reviewed all the cases. The ellipsoid formula was calculated based on renal dimensions

Table 2. Patient characteristics at last follow-up.

	n	Median	SD	Min	Max	Q1	Q3
Age (y)	12	27.6	8.5	20.8	45.0	23.7	39.9
Weight (kg)	12	56.3	19.8	33.2	106.5	46.5	74.1
Height (cm)	12	159.0	7.6	149.0	173.0	151.3	163.8
Serum creatinine (umol/L)	12	62.0	26.8	19.0	113.0	43.3	82.8
GFR (ml/min/1.77 m^2)	12						
MDRD	12	122.8	94.2	48.8	394.7	86.2	166.2
CKD-EPI	12	123.0	31.2	52.0	165.0	93.3	136.0
CockG	12	121.6	84.7	47.2	314.3	76.1	174.3
Kidney volume (cm^3)							
Ellipsoid formula							
Right kidney	11	538.4	495.1	256.6	1880.1	313.4	776.7
Left kidney	10	540.0	966.6	180.7	2864.2	267.9	1213.1
Total renal volume	12	973.9	1185.4	367.0	4376.5	583.8	1812.1
3D reconstruction							
Right kidney	11	454.7	537.8	232.7	1933.8	344.7	1016.9
Left kidney	10	558.1	764.1	166.6	2403.0	253.7	1001.4
Total 3D renal volume	12	971.9	1112.6	399.3	4336.8	495.0	1897.5

3D=3-dimensional; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease equation; Q1=25 percentile; Q3=75 percentile.

Table 3. Correlation between renal volume and estimated glomerular filtration rate at last follow-up.

		Cr	MDRD	CKD EPI	CockG
Total kidney volume by ellipsoid formula	Pearson correlation	.029	.074	-.034	-.203
	P value (2-tailed)	.930	.820	.916	.527
Total kidney volume by 3D reconstruction	Pearson correlation	-.150	.199	.145	-.098
	Sig. (2-tailed)	.642	.535	.653	.761

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; Cr=Serum creatinine; MDRD=Modification of Diet in Renal Disease equation.

Table 4. Comparison between patients who underwent any intervention to control bleeding versus no intervention.

	No Intervention						Intervention to control bleeding						*P*
	n	**Mean**	**Median**	**Min**	**Max**	**SD**	**n**	**Mean**	**Median**	**Min**	**Max**	**SD**	
Age (yrs)	6	26.9	25.8	20.8	35.3	5.3	6	33.9	34.4	21.3	45.0	10.2	.166
Weight (kg)	6	68.1	68.5	33.2	106.5	24.5	6	53.4	50.0	42.0	74.4	11.6	.213
Height (cm)	6	158.7	157.0	149.0	173.0	8.7	6	158.8	160.1	150.0	168.5	7.1	.980
Kidney volume (cm^3)													
Ellipsoid formula													
Right kidney	6	600.0	494.5	256.6	1264.1	373.7	5	773.8	557.8	289.6	1880.1	646.2	.589
Left kidney	6	506.1	540.0	180.7	785.3	238.1	4	1479.8	1434.4	186.1	2864.2	1396.5	.123
3D reconstruction													
Right kidney	6	651.2	448.1	232.7	1416.5	462.8	5	788.0	530.5	259.7	1933.8	665.2	.697
Left kidney	6	516.5	558.1	166.6	672.2	184.2	4	1219.8	1126.4	223.5	2403.0	1139.9	.165
Serum creatinine (umol/L)	6	51.5	47.0	19.0	92.0	27.2	6	74.3	71.0	50.0	113.0	22.9	.147
GFR (ml/ min/1.77 m^2)													
MDRD	6	193.0	150.6	90.5	394.7	113.5	6	96.2	94.0	48.8	136.1	31.7	.072
CKD-EPI	6	133.8	131.5	97.0	165.0	24.8	6	99.0	101.5	52.0	127.0	28.3	.047
CockG	6	192.6	157.9	115.5	314.3	90.2	6	88.3	83.6	47.2	126.3	33.3	.024

*t test for comparison of means (2-tailed) Equal variances assumed.

3D=3-dimensional; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease equation.

Table 5. Change between first visit and last follow-up.

	First visit						Last follow-up visit						*P*
	n	Mean	Median	SD	Min	Max	n	Mean	Median	SD	Min	Max	
Age (y)	8	25.8	24.8	8.9	10.6	41.7	8	30.9	26.5	10.2	20.8	45.0	.031
Weight (kg)	8	59.1	54.5	20.7	41.0	103.7	8	62.5	54.9	21.5	42.0	106.5	.468
Height (cm)	8	155.8	158.0	9.4	138.0	168.5	8	157.6	158.0	6.5	150.0	168.5	.351
Kidney volume (cm^3)													
Ellipsoid formula													
Right kidney	7	586.4	463.8	325.0	232.0	1135.2	7	661.9	450.6	562.6	289.6	1880.1	.544
Left kidney	6	893.3	606.3	795.3	177.0	2362.3	6	1151.7	534.1	1201.8	186.1	2864.2	.319
Total kidney volume	8	1183.1	921.3	729.2	463.8	2362.3	8	1442.9	853.3	1418.4	367.0	4376.5	.367
3D reconstruction													
Right kidney	7	594.6	518.9	300.6	276.3	1090.1	7	675.7	454.7	576.7	259.7	1933.8	.571
Left kidney	6	998.5	739.7	823.7	264.5	2512.4	6	1003.8	571.9	945.1	223.5	2403.0	.982
Total kidney volume 3D	8	1269.1	972.6	775.1	415.5	2512.4	8	1344.1	967.0	1306.7	454.7	4336.8	.794
Serum creatinine (umol/L)	8	66.5	68.0	15.1	48.0	84.0	8	64.8	62.0	26.4	31.0	113.0	.740
GFR (ml/min/1.77 m^2)													
MDRD	8	103.3	109.9	25.7	72.7	140.5	8	125.3	113.3	63.4	48.8	249.7	.278
CKD-EPI	8	106.5	113.0	21.8	80.0	131.0	8	111.1	118.0	33.1	52.0	156.0	.587
CockG	8	114.2	97.0	60.5	62.1	251.6	8	142.0	111.7	103.5	47.2	314.3	.298
Duration (days)							8	1462.8	1266.0	1403.5	33.0	3133.0	

*Paired samples *t* test (2-tailed).

3D=3-dimensional; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation; CockG=Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease equation.

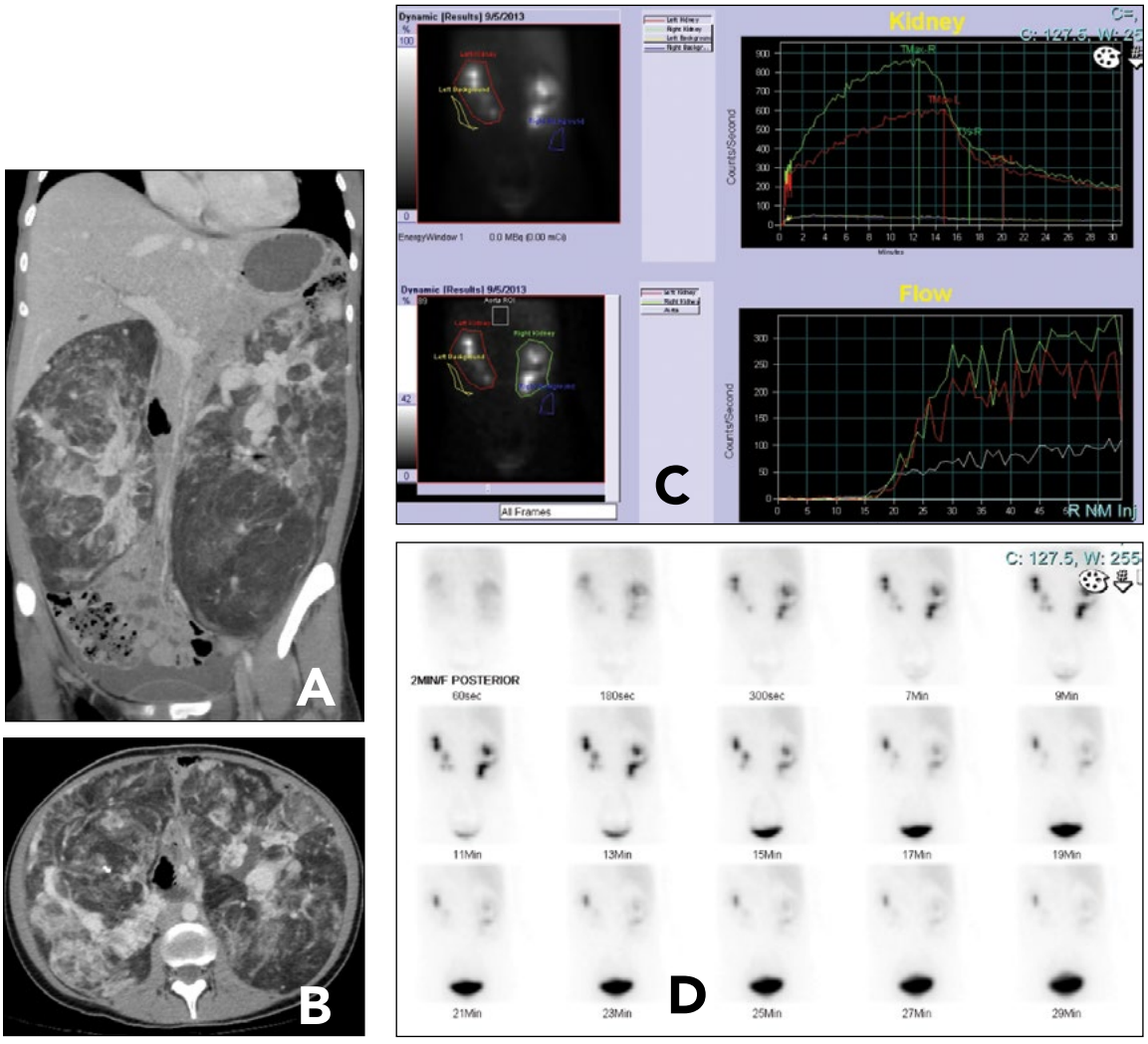

Figure 1. An imaging study in 2013 of a 31-year- old female with bilateral large renal angiomyolipoma. She had selective arterial embolization for active bleeding twice on the right side (2005 and 2008) and once on the left side (2008). **A.** Coronal CT image shows the right kidney measuring 20.9x10.4 cm and left kidney 22.7x10.6 cm craniocaudally and transversely respectively. **B.** A transaxial CT image showing right kidney dimensions of 14.8x9.5 cm and left kidney dimensions of 18.3x10.5 cm. **C.** Technetium MAG3 diuretic renogram showing adequate perfusion and cortical uptake with slow transit and progressive accumulation of tracer in the dilated collecting system (delayed excretion showed good response to furosemide at 10 minutes). **D.** Static images of the renogram. Serum creatinine at the time of the study was 54 umol/L and eGFR >60 mL/min/1.77 m^2. MAG3=mercaptoacetyltriglycine.

measured by two urologists (RS and WAK) while the 3D reconstruction was performed by the radiologist. Both methods accurately reflect renal volume.[16,17] The two results were highly correlated, similar to previous studies.[18]

The median renal volume in our study was 455 mL for the right side and 558 mL for the left side. The normal renal volume differs between sexes; the mean renal volumes determined by CT were 156.5 mL and 193.1 mL for female and male subjects, respectively.[19] Volume measurement with MRI showed similar results of 154 mL and 202 mL, respectively.[20] In our study, women had a median renal volume three times the normal value of an adult on the left side and four times on the right side. These figures reflect a high AML tumor burden. Only 25% of all kidneys had a volume equal to or less than 345 mL on the right side and 254 mL on the left. Still, these kidneys demonstrated numerous AML lesions on imaging. The smallest kidney in the series belonged to a female patient (volume 166.6 mL), and had innumerable small subcentimetric AMLs reflecting a significant tumor burden. Inclusion

of the few patients with small kidneys does not seem to have significantly affected the GFR results.

Renal function determination

We determined renal function using the eGFR formulas as an accepted alternative to the more accurate yet difficult to implement method of exogenous substance clearance.[11-14] The results of the three formulas correlated significantly with each other. By definition, all patients are classified as having CKD stages 1-5 on the basis of kidney structural changes seen on imaging, regardless of the eGFR.[21] CKD stages 1 and 2 according to this definition are associated with eGFR ≥90 mL/min/1.77 m^2 and ≥60 mL/min/1.77 m^2, respectively. Significant CKD (stages 3-5) is diagnosed when the eGFR is below 60 mL/min.[21] Most of our patients (91.7%), according to this definition, had normal renal function at the last follow-up. The three patients with an eGFR <90 mL/min/1.77 m^2 had a total of three total nephrectomies, one contralateral partial nephrectomy, and three selective arterial embolizations. The reported eGFR reflects total renal function. It could be argued that the contralateral renal units contributed to normal renal function when the affected kidney was poorly functioning. In this series, several factors seem to refute this assumption. First, only 25% of renal units had a volume less than 254-345 ml. Second, all kidneys had numerous AML lesions. Third, three patients had a solitary kidney following total nephrectomy for bleeding. None had impaired renal function. However, a better way to emphasize our observations is to document split renal function using radioisotope scanning. Some patients underwent MAG3 scanning (**Figure 1C, D**). Even with huge bilateral AMLs, the scan shows increased blood flow due to high vascularity of the lesions and preserved renal function.

Another method to determine split renal function is to calculate the renal volume. Several studies showed that in normal kidneys, the relative renal tissue volume determined by CT correlated well with split renal function calculated from scintigraphy studies. The correlation was strong in healthy kidney donors,[22] and in the case of chronically obstructed kidneys.[23] It is not known whether this principle applies to kidneys with AMLs. In our series, there was no significant correlation between total renal volume and eGFR. This was probably because the increase in volume of AML-affected kidneys was due to the volume of the nonfunctioning tumor rather than an increase in healthy tissue volume. Another factor was the actual eGFR figures above 60, which though indicating normal renal function, may not correlate well with true GFR.

Effect of AML on renal function

Previous reports stressed that AMLs were associated with impaired renal function and contributed to mortality due to renal failure. Renal failure was labeled as the second cause of death in TSC patients after neurological complications.[6] A survey of 260 dialysis units in France identified 65 patients with TSC and chronic renal failure.[7] Eight patients died as a consequence of renal failure or its treatment. However, the authors estimated the prevalence of TSC and renal failure in France to be around 0.7 per million and 1% among patients with TSC. It is interesting that 41.5% of patients had a nephrectomy. Several case reports linked TSC AMLs with renal failure.[24-29] These reports suggested that the mechanisms underlying renal failure included hyperfiltration injury leading to focal glomerulosclerosis and reduction of nephron mass by tumor invasion, cysts, and surgery. A more recent retrospective study reported more frequent CKD stages 3-5 in a TSC patient cohort treated in general practice than in another cohort at all ages; the frequency peaked at ages greater than 65 years (42% vs. 23%).[30] In a retrospective, longitudinal cohort study of TSC patients treated at a specialty center in the Netherlands, 16% of patients younger than 70 years old reached CKD stage 3 or higher during follow-up.[5] In contrast, in a reference population of non-TSC patients, only 3% had CKD stage 3 or higher. On the other hand, other studies of large numbers of patients reported normal renal function despite numerous interventions to prevent or control bleeding.[2,3] We observed that patients with huge bilateral AML such as that shown in **Figure 1**, still maintained normal renal function. It is interesting that the only situation when there was a significant deterioration of renal function in our series was in patients who underwent an intervention to stop bleeding. This is in agreement with the findings of the Dutch study, which showed that among other factors (age, AML size and number, female gender, and TSC2 gene mutation) significantly associated with advanced CKD stages, having undergone renal embolization was a likelihood.[5] The embolization status for patients with CKD stages 1-5 was 25.4, 47.8, 59.3, 68.0, and 77.8%, respectively (P<.001).[5] We speculate that AML burden itself does not impair renal function, but the intervention does. This is in agreement with data from several studies showing a significant number of nephrectomies,[7] and embolizations,[5] in patients with renal impairment. We postulate that maintenance of normal renal function in such patients is attributable to the high vascularity supplying the kidney, lack of infiltration/replacement of AML lesions with normal func-

tioning renal tissue, and absence of compression exerted by these lesions on renal parenchyma. The lack of compression might be due to the free expansion of the lesions into the abdominal cavity, which is not confined by the renal capsule and the soft consistency of the fat-rich lesions.

In conclusion, TSC AML renal tumors may attain a large size and are subjected to numerous interventions. Potentially, some interventions can affect renal function. However, despite interventions in the vast majority of our patients, follow-up over several years did not show significant change in the eGFR, irrespective of tumor burden.

Acknowledgment

The authors appreciate the valuable help of Ms Nora Alsoraya 3D Imaging Specialist. No funding or other financial support was received for this project.

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