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CASE REPORT

Successful treatment with sirolimus for an angiomyolipoma mimicking renal cell carcinoma in a transplanted kidney

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Summary

Angiomyolipoma (AML) is a benign mesenchymal tumor composed of blood vessels, smooth muscle, and mature adipose tissue. AMLs in the kidney allografts are rare. We report a case of AML that was incidentally found 1 year after transplantation. Abdominal computed tomography showed a 4-cm renal tumor with contrast enhancement and an early washout pattern, resembling a renal cell carcinoma. Tumor biopsy proved a lipid-poor AML. Tumor diameter decreased to 2.4 cm after 6 months of treatment with sirolimus. Sirolimus not only reduces tumor size, but also benefits a transplant patient who needs immunosuppression.

Introduction

Angiomyolipoma (AML) is a benign mesenchymal tumor composed of blood vessels, smooth muscle, and adipose tissue. AML in transplanted kidneys is rare, and with only few cases reported [1–4]. Mammalian target of rapamycin (mTOR) inhibitors are emerging treatment strategies for AML, especially tuberous sclerosis (TSC)-related AML [5–7]. We report a case of AML that developed 1 year after renal transplantation; it was successfully treated with sirolimus, an mTOR inhibitor.

Case report

A 37-year-old woman with end-stage renal disease due to lupus nephritis and polycystic kidney disease underwent deceased donor kidney transplantation in October 2012. The donor was a 38-year-old man who died of intracranial hemorrhage. The patient had a high panel-reactive antibody (PRA) level (Class I: 100%, Class II: 30%), but human leukocyte antigen typing showed zero mismatch to the donor. Abdominal ultrasonography results of the donor were normal. The operation was smooth, without complications. The patient started receiving triple immunosuppressive therapy including tacrolimus, mycophenolate mofetil (MMF), and prednisolone. Amlodipine was prescribed for her blood pressure control. Two weeks after the operation, the serum creatinine level was 1.3 mg/dl.

The patient was doing well without significant discomfort. Owing to a history of a liver nodule, abdominal computed tomography (CT) was performed in October 2013. The CT images showed a 1-cm enhancing lesion in the liver, with no change from that observed previously. The nodule was thought to be a small hemangioma.

A 4-cm tumor in the graft kidney was incidentally found on the CT images. It was slightly hyperdense on plain film and contrast-enhanced, with an early washout pattern (Fig. 1a–c). The characteristics on CT suggested a renal cell carcinoma.

Although nephron sparing surgery is relatively safe and is considered appropriate for small tumors of transplanted kidneys because of its good long-term functional and oncological outcomes [8], the patient was concerned about the potential risks associated with anesthesia and surgery and decided to undergo a biopsy. CT-guided biopsy showed that the specimen was 1 × 0.1 × 0.1 cm and composed of kidney tissue with disorganized proliferating spindle cells with eosinophilic to clear cytoplasm. The kidney tissue had compression fibrosis, but no inflammation or signs of rejection were found (Fig. 2a). Few adipocytes were observed, with large lipid droplets in the cytoplasm (Fig. 2b). Immunohistochemistry stains showed co-expression of HMB-45, actin (Fig. 2c), and microphthalmia-associated transcription factor (Fig. 2d). These features are typical of lipid-poor AML.

Owing to the absence of tumor-related symptoms and the relatively low risk of bleeding, immediate surgery or angiographic catheter embolization was not required. Sirolimus [1 mg once daily (QD)] was added to the patient's medication regimen and titrated to 2 mg QD to reach 5–8 ng/ml in the serum. Simultaneously, MMF was gradually tapered (decreased from 360 mg twice daily to 180 mg QD) and then discontinued 3 months later to avoid over-immunosuppression.

Repeat abdominal CT performed 3 and 6 months later showed shrinkage of the tumor from 4.0 to 2.5 and 2.4 cm, respectively (Fig. 3a–c). The volume of the tumor was estimated as follows: The pretreatment and post-treatment CT images were reconstructed using thin-section (0.7 mm) images. Regions of interest were outlined by the same radiologist using a hand-operated cursor, with the naked eye. The sum of all the cross-sectional areas in square millimeters multiplied by 0.7 mm yielded the estimated volume of the tumor.

We found that the estimated tumor volume decreased from 15.8 to 5.1 cm^3 (67.7%) and 4.9 cm^3 (68.9%) after 3 and 6 months of treatment, respectively. One year post-mTOR inhibition, the serum creatinine level was 0.88 mg/dl, and no significant adverse effects such as oral ulcers, lower limb edema, or dyslipidaemia were observed.

Discussion

Angiomyolipoma is a common but benign renal tumor. It is usually single and unilateral, but multiple and bilateral lesions are sometimes found, particularly in association with TSC. AML in a kidney allograft is rare, with only a few cases reported (Table 1) [1–4].

Knowing the fat content of a kidney tumor is important for establishing a diagnosis of AML. Tissue attenuation of −10 Hounsfield units (HU) is an indicator of fat on unenhanced CT [9]. However, approximately 4–5% of AMLs are lipid poor**.** These tumors appear hyperdense on non-contrast CT. With contrast, they resemble clear cell renal cell carcinomas, with prominent enhancement in the corticomedullary phase and a slight washout in the nephrographic phase [10]. In the current case, a renal biopsy revealed <25% fat cells per high-power field (Fig. 2b), indicating a lipid-poor renal AML. Tumor biopsy is crucial to rule out malignancy and prevent unnecessary nephrectomy, especially for a renal transplant patient who had high PRA levels and who underwent zero-mismatched kidney transplantation.

Current treatment options for AML focus on conserving kidney function and preventing potentially fatal hemorrhage. Treatment options include observation, total or partial nephrectomy, and embolization, depending on the clinical condition. Alternative ablative techniques such as radiofrequency and cryoablation have been reported safe and effective [11,12]. Recently, mTOR inhibitors have been studied in open-label trials, mainly for TSC-related AMLs [5–7]. TSC is caused by mutations in the *TSC1* or *TSC2* suppressor genes, resulting in increased mTOR activity. Kenerson *et al.* [13] found increased levels of

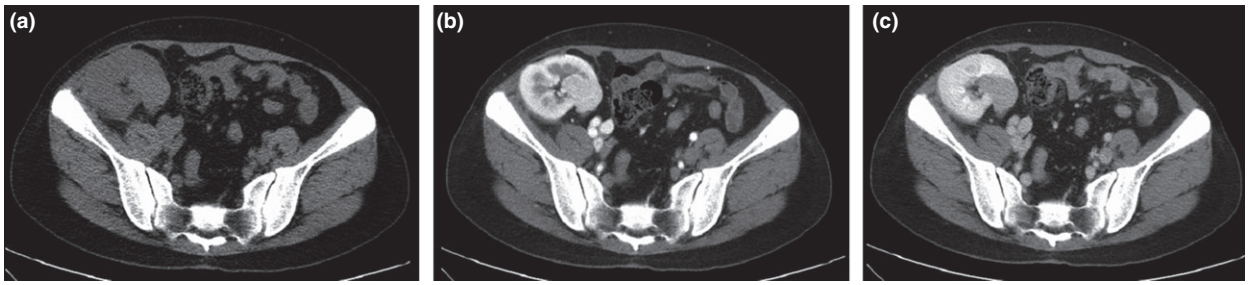

Figure 1 Abdominal computed tomography of the patient 1 year after kidney transplantation. (a) 4-cm tumor in the kidney allograft, unenhanced phase. (b) Homogenous enhancement in the corticomedullary phase. (c) Early washout pattern in nephrographic phase.

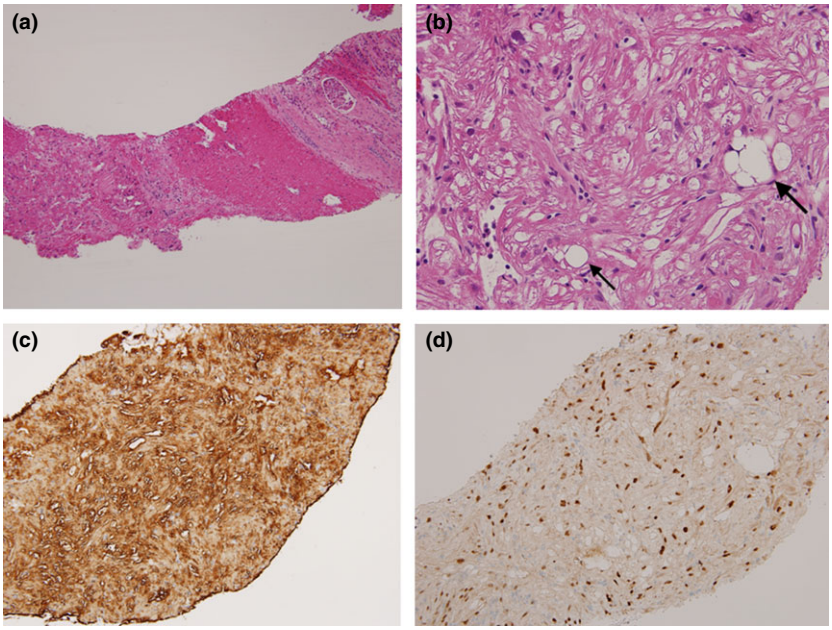

Figure 2 Renal biopsy of the tumor: (a) Compression fibrosis of renal tissue, without inflammation or signs of rejection (hematoxylin and eosin, magnification ×40). (b) Disorganized proliferating spindle cells with eosinophilic to clear cytoplasm, with scanty fat cell droplets, indicated by dark arrows (hematoxylin and eosin, magnification ×400). Immunohistochemistry shows positive staining for actin (c) (magnification ×200) and microphthalmia-associated transcription factor (d) (magnification ×200).

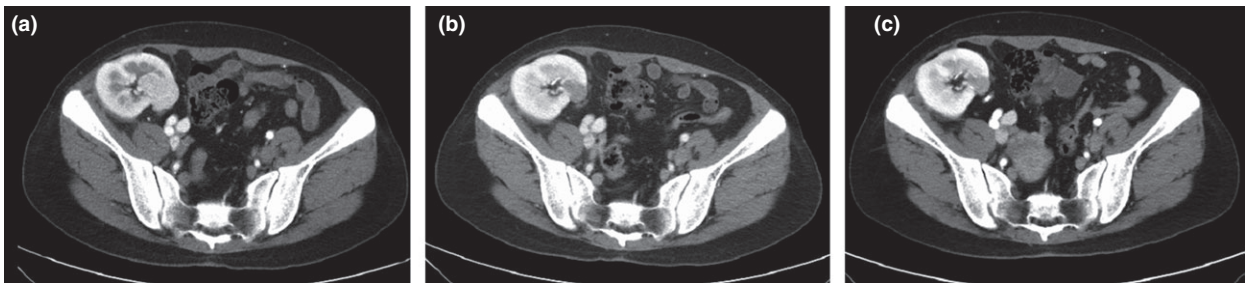

Figure 3 After 3 and 6 months of mTOR inhibitor treatment, abdominal computed tomography in the corticomedullary phase revealed tumor size decreased from 4 cm (a) to 2.5 cm (b) and 2.4 cm (c), respectively.

Table 1. Previous case reports of angiomyolipoma in kidney allografts.

Cases	Mosunjac *et al.* [2]	Colman *et al.* [1]	Lappin *et al.* [3]	Roozbeh *et al.* [4]
Discovery	Incidental finding on postmortem	Incidental finding on graft biopsy (day 4 post-transplantation)	Routine subcapsular biopsy (intraoperatively)	Incidental finding on routine ultrasonography (3 years post-transplantation)
Tumor characteristics		Four tumors, 1 cm each in diameter, mimicking malignancy	Ultrasonography showing 4-mm residual tumor or hematoma after graft biopsy	Hyperechoic mass measuring 7.7 cm
Treatment		Nephrectomy	Observation	Partial nephrectomy
Outcome			Stable, 7-year follow-up	Stable, 4-year follow-up

phospho-p70S6K, a marker of mTOR activity, in non-TSC AMLs. Therefore, mTOR inhibitors may also be effective in non-TSC-related AMLs.

Our case was an incidentally detected AML after renal transplantation. Typical TSC lesions such as cortical tubers, subependymal nodules, or subependymal giant cell tumors

were not mentioned in the donor's CT report, but these features may be difficult to identify after massive intracranial hemorrhage with perifocal edema. The donor had no history of seizure and no specific family history of systemic disease. Non-TSC-related AML in the graft is the likely diagnosis, but investigation of the status of the *TSC* gene in the kidney graft would be required to confirm this diagnosis.

Treatment with mTOR inhibitors can not only decrease the size of AML in a kidney graft but also have a beneficial effect as an immunosuppressant. It has the potential for sparing more nephrons compared with embolization or partial nephrectomy. In our case, after adding an mTOR inhibitor to the immunosuppressive regimen, we gradually tapered the dose of MMF and discontinued MMF after 3 months of concomitant treatment. We continued using tacrolimus but replaced MMF with sirolimus to avoid acute rejection during the medication switch period.

It is particular noteworthy that mTOR inhibitors may enhance calcineurin inhibitor-related toxicity, especially cyclosporine. High doses of tacrolimus combined with sirolimus have less deleterious effect on renal function in comparison with high doses of cyclosporine combined with sirolimus in the short term, but focal tubular atrophy and profibrotic inflammatory mediators were manifested in the long term in animal studies [14]. Therefore, we closely monitored the serum tacrolimus level, which was maintained at approximately 7–10 ng/ml. We also maintained the serum sirolimus level at 5–8 ng/ml, and monitored the lipid profile, platelet count, and urine proteins to detect any early signs of mTOR inhibitor toxicity. To date, there has been no acute rejection and serum creatinine is stable.

The maintenance trough level of sirolimus in previous trials for TSC-related AMLs was 3–15 ng/ml [5–7]. In our case, the level was maintained at 5–8 ng/ml, the same target for an immunosuppressive effect. The mean decrease in AML size after sirolimus treatment was 30% in Dobora's trial and 39% in Davies' trial, calculated by the sum of longest diameters of tumor [5,6]. This result was comparable to our case, which was 40.0% decreased. Volume reduction estimated by software program was 66% in Cabrera's trial, similar to our case, which was 68.9% [7]. However, our patient was reevaluated 6 months after treatment, which was a much shorter time than that in the aforementioned studies (12 months). The significant effect of mTOR inhibitor in our case may be due to the relatively higher vascularity of the lipid-poor tumor. A highly vascularized tumor may have elevated vascular endothelial growth factor secretion and increased mTOR activity.

In conclusion, an AML in a transplant kidney was successfully treated with an mTOR inhibitor. Such treatment not only reduces tumor size, but also benefits a transplant patient who needs immunosuppression. The dual effect of mTOR inhibitors may have an important role in the treatment of AML in a transplant kidney, especially in highly vascularized, lipid-poor tumors.

Authorship

H-FC: drafted the article and involved with patient care. M-CW: contributed the manuscript and involved with pathology report. J-RL and H-CH: contributed the manuscript and involved with transplantation. K-HS: drafted, revised the article and involved with patient care.

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