Contrast-enhanced ultrasound findings of post-transplant lymphoproliferative disorder in a transplanted kidney: A case report and literature review

Alyssa Lampe[1], Vinay A Duddalwar[1], Hooman Djaladat[2], Manju Aron[3], Mittul Gulati[1]

1. Department of Radiology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

2. Department of Urology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

3. Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

* **Correspondence:** Mittul Gulati, Department of Radiology, USC Keck School of Medicine, 1500 San Pablo Street, 2nd Floor Imaging, Los Angeles, CA, 90033, USA
(*mittul.gulati@med.usc.edu*)

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ABSTRACT

Post-transplant lymphoproliferative disorder occurs in approximately one percent of kidney transplant recipients. We evaluated a seventy-seven year-old man with a solid mass in his transplant kidney. On contrast enhanced ultrasound, the mass enhanced but remained persistently hypovascular throughout exam. The enhancement pattern of the mass differed from that typical of clear cell renal cell carcinoma, the main differential diagnosis. Final pathology after partial nephrectomy confirmed post-transplant lymphoproliferative disorder. This is the first report of contrast enhanced ultrasound findings in a renal mass diagnosed as post-transplant lymphoproliferative disorder. Contrast enhanced ultrasound has a promising role in imaging of renal masses, particularly relevant in transplant patients due to the lack of nephrotoxicity.

CASE REPORT

CASE REPORT

A seventy-seven year-old Hispanic male presented nine years after renal transplant in a hypertensive crisis. Non-enhanced computed tomography (NECT) showed a solid, centrally hypodense renal mass measuring approximately 3 cm in the lower pole of the transplanted kidney (Figure 1). The patient's renal function precluded contrast-enhanced computed tomography (CECT).

Grayscale and color Doppler ultrasound (US) and contrast-enhanced ultrasound (CEUS) were performed. Grayscale US demonstrated a hypoechoic, solid mass in the lower pole transplant renal cortex measuring 2.1 cm x 3.3 cm x 2.8 cm, with minimal flow on color Doppler exam (Figure 2). For CEUS, multiple 0.2 cc boluses of Definity® (Perflutren lipid microspheres, Lantheus Medical Imaging) were injected into the patient via an antecubital route, each followed by a 10 cc flush of saline. Continuous real-time CEUS imaging was performed using low mechanical index settings. Following administration of contrast, the mass showed early peripheral

enhancement in the corticomedullary phase. Subsequently, the mass showed progressive, predominantly peripheral, enhancement during the parenchymal phase, but remained hypovascular to normal renal parenchyma throughout CEUS exam. The center of the mass showed no enhancement, consistent with necrosis (Figure 3).

At the same setting as CEUS, core needle biopsy of the renal mass was performed (Figure 4). Multiple 18-gauge core needle specimens were obtained, with ultrasound guidance and cytotechnologist confirmation of specimen adequacy by touch preparations.

The initial pathology interpretation of the core needle biopsy favored clear cell renal cell carcinoma (ccRCC). Based on this initial pathology, the patient subsequently underwent partial nephrectomy of the transplant kidney. Final pathology from the partial nephrectomy specimen returned post-transplant lymphoproliferative disorder (PTLD), specifically diffuse large B cell lymphoma (DLBCL), Epstein-Barr virus (EBV) positive. Re-review of the core needle biopsy by the pathology department confirmed that PTLD (DLBCL) was the correct diagnosis on the biopsy specimens as well.

Pathologic evaluation:

Microscopic evaluation of the renal biopsy showed predominantly coagulative necrosis with a few islands of viable tumor separated by vascular spaces. The tumor cells showed predominant clearing of the cytoplasm (Figure 5). This cytoplasmic clearing, along with the sinusoidal vascular spaces, raised the possibility of a clear cell renal cell carcinoma. No immunohistochemical stains were performed by the pathologist.

Subsequently, the partial nephrectomy specimen showed a poorly circumscribed, multinodular, necrotic tumor measuring 3.9 cm in greatest dimension. On microscopic examination, the tumor nodules were composed of sheets of monomorphic cells with moderate eosinophilic cytoplasm with focal cells showing cytoplasmic clearing (Figure 6). The tumor cells had vesicular nuclear chromatin, variably irregular nuclear contours and several distinct nucleoli. Large areas of infarction necrosis were identified within the tumor with the adjacent renal parenchyma showing interstitial infiltrate of small lymphocytes. The tumor cells were positive for CD20 (Figure 7) and in-situ hybridization showed positivity for EBER (Epstein- Barr encoded RNA) (Figure 8). The tumor cells were negative for CD10 and BCL6.

The morphological and immunophenotypic profile was consistent with a monomorphic post-transplant lymphoproliferative disorder (PTLD); diffuse large B-cell lymphoma with a non-germinal center immunophenotype.

The patient was initially treated by decreasing his immunosuppressive medications, followed by systemic chemotherapy for six weeks. Following treatment, the patient's drenching sweats and rigors resolved, and he gained four pounds. On follow-up one year after his transplant kidney partial nephrectomy, the patient was doing well, and was not on dialysis, with renal function similar to his pre-operative baseline.

DISCUSSION

Etiology & demographics

PTLD is a protean entity, with the term encompassing any lymphoid malignancy arising after transplantation (1). The disorder is rare, occurring in approximately one percent of renal transplant recipients (Table 1) (2). Almost all cases of PTLD are associated with Epstein-Barr virus (EBV) (3). PTLD is more prevalent in males, with a male to female gender ratio of 1.23:1. The disease has a bimodal age distribution, with peaks in young (less than 20 years of age) and older (greater than 50 years of age) groups (4). Presenting symptoms of PTLD include fevers, night sweats, weight loss, and lymphadenopathy (5). The renal allograft is a common site of PTLD after renal transplantation, affected in 46 of 135 PTLD patients (34%) in one meta-analysis. Renal allograft involvement was secondary only to lymphadenopathy (present in 53 of 135, or 40% of patients) as a site of PTLD (6).

Clinical and Imaging findings

Although the renal allograft is a common site for PTLD after renal transplant, few studies have described the imaging findings of this entity. An early paper by Claudon et al. found that US could suggest PTLD by detecting urinary obstruction associated with adenopathy, or an ill-defined, newly visualized mass, but that CECT or MRI were superior in detection and follow-up of the disease (7). In a series by Kew et al., US showed a heterogeneous mass at or adjacent to the renal hilum in 10 of 14 patients with PTLD after renal transplant. Five of the ten patients with a hilar mass also showed hydronephrosis on US (8).

In a case report by Moir et al., US in a renal transplant recipient demonstrated mild hydronephrosis and numerous hypoechoic parenchymal lesions, felt to be cystic, measuring up to 2 cm. The lesions were initially presumed to represent fungus balls, and the patient was empirically treated for infection, without improvement. Subsequent biopsy of the renal lesions revealed PTLD (9).

Imaging findings of renal lymphoma, a broader disease category, have been described more frequently than has renal PTLD. Renal lymphoma typically presents as multiple bilateral masses (60%), direct extension from retroperitoneal nodes (25%), or as a solitary mass in one kidney (15%). Renal lymphoma is typically hypoechoic on gray scale US, and hypovascular throughout contrast-enhanced exam on both CT and MRI. On MRI, renal lymphoma is T1 isointense, T2 hypointense relative to normal renal cortex (10). Additional typical imaging features on CECT and MRI include size < 3 cm, lack of spherical shape, "infiltrative" growth, multiplicity, bilaterality, and lack of encapsulation or calcifications (11).

In our case, we utilized CEUS, which is valuable in characterizing solid renal masses because it allows for continuous visualization of enhancement. CEUS relies on intravenous injection of encapsulated microbubbles of gas

smaller than a red blood cell, but much larger than particles used as CECT and MRI agents. The microbubbles act as pure intravascular contrast agents (12). The microbubbles demonstrate non-linear oscillation between 3 and 5 MHz, which is in the diagnostic range of US frequencies. After circulating for several minutes in the blood pool, the microbubbles dissolve. Internal gas is exhaled, and the coating, which may be protein, lipid, or polymer, is metabolized, primarily by the liver (13).

Imaging advantages of CEUS include ability to detect microvasculature which can be overlooked by Color and Power Doppler US. While Doppler US can image blood vessels as small as 100 micrometers, CEUS can show vessels as small as 40 micrometers (14). In addition, CEUS allows for high temporal resolution, with continuous dynamic imaging after injection as opposed to the intermittent static acquisitions possible with CECT and MR.

CEUS relies on the principle of phase inversion. Two ultrasound pulses with 180 degree phase difference are sent consecutively. Echoes returning to the transducer are summated by the software, and as a result the linear echoes from body tissues null each other. In this manner, tissue signals are almost entirely cancelled out, but contrast agent perfusing the tissues has a strong signal. Low mechanical index settings allow detection of contrast agent and minimize microbubble destruction (15).

For CEUS, complete real-time video clips of the examination are stored, with images acquired continuously for at least 2 minutes after contrast administration.

Renal CEUS exam contrast phase terminology is controversial, with numerous naming schemes used in literature. In practice, the following phase terms are typically used: early, or corticomedullary (enhancing cortex with medullary pyramids not yet perfused, approximately 15-30 seconds post injection); parenchymal, or nephrographic (homogenously enhancing renal parenchyma, approximately 30-70 seconds post injection); and delayed (>70 seconds post injection). Interpretation relies on evaluating the enhancement pattern of the lesion relative to the adjacent normal kidney.

As opposed to the iodinated contrast used for CECT, or the gadolinium used for magnetic resonance imaging (MRI), the contrast agents used for CEUS are non-nephrotoxic. Many nephrologists prefer to avoid nephrotoxic agents in renal transplant recipients (16). Unlike noncontrast CT or MRI, CEUS accurately demonstrates the enhancement pattern in solid renal masses in transplant recipients. A recent study by Barr et al. found that CEUS has high sensitivity (100%) and specificity (95%) in the characterization of indeterminate renal masses (17).

This is the first report we are aware of describing the findings of renal PTLD using CEUS. In our patient, the discrete, solitary renal mass which proved to be lymphoma (specifically, PTLD), enhanced, but remained persistently hypovascular throughout the entire CEUS exam. This enhancement pattern on CEUS differed markedly from that of ccRCC, the main differential diagnosis, which shows avid early hyperenhancement (18).

Our results support the recent findings of Trenker et al., the only series to date describing CEUS of renal lymphoma. The majority of patients in that series presented with an infiltrative growth pattern of lymphoma rather than a discrete mass. However, the lymphomas which presented as masses were isovascular or hypovascular to renal parenchyma in arterial phase, and all were hypovascular in parenchymal phase (19).

Treatment & Prognosis

Some authors recommend excision of PTLD prior to initiation of systemic chemotherapy. However, most oncologic literature suggests that reducing immunosuppression, combined with systemic chemotherapy, can result in long term progression-free survival without surgery (20). The overall two year survival rate for renal PTLD ranges from 70-83% (6).

Evaluation of a new solid mass arising in a transplant kidney often includes biopsy. In our patient, initial pathology misinterpretation of the technically adequate, 18-gauge core needle biopsy specimens as ccRCC, rather than PTLD, led to partial nephrectomy. Immunohistochemical stains which would have confirmed lymphoma were not performed on the initial biopsy specimen, but only done after partial nephrectomy.

Differential Diagnosis

The primary differential for a solid mass in a transplant kidney is PTLD versus ccRCC (21). Less prevalent differential diagnoses include angiomyolipoma. The imaging features of these differential diagnoses are described below and summarized in Table 2.

Clear cell renal cell carcinoma (ccRCC)

CcRCC, by far the most common RCC subtype, hyperenhances early (in the arterial, or corticomedullary phase), and hypoenhances later (in the parenchymal, or nephrographic phase) on both CECT and MRI. Necrosis, hemorrhage, and calcification are common. On MRI, ccRCC is T1 isointense and T2 hyperintense; subtraction imaging may be useful to confirm the presence of subtle enhancement. On US, ccRCC is often hyperechoic when small (less than 2 cm). Larger ccRCC are typically hypoechoic or heterogeneous, exophytic, and can have anechoic central necrosis (22). On CEUS, ccRCC similarly demonstrates avid early arterial hyperenhancement and parenchymal phase wash out relative to normal renal cortex, with a peri-lesion rim of enhancement ("pseudocapsule") (18). This avid early enhancement differentiates ccRCC from the persistent hypoenhancement of PTLD throughout CEUS exam.

Angiomyolipoma (AML)

On US, typical AMLs are homogenously hyperechoic to renal cortex when small due to fat content (23). On CT and MRI, measurable fat density in a solid renal mass is diagnostic of AML. Larger tumors are typically heterogeneous, with fat, vessels, and soft tissue components. Less than 5% of AMLs are lipid-poor, and present a diagnostic dilemma due to their

lack of measurable fat (24). Lipid-poor AMLs are suggested by high density on NECT, as well as T2 hypointensity on MRI (25). On CEUS, AMLs have been described as homogenous, hypoenhancing relative to renal parenchyma, and displaying persistent (greater delayed) enhancement compared with ccRCC (26).

Conclusion

A description of CEUS in renal PTLD has, to the best of our knowledge, not previously been reported. In our patient, PTLD in a renal allograft presented as a focal intra-renal mass. CEUS showed an enhancing but persistently hypovascular lesion. The CEUS findings in this case were not typical of ccRCC, which normally shows avid early hyperenhancement, and core needle biopsy was performed. Initial pathology misinterpretation of the biopsy specimen as ccRCC led to partial nephrectomy. Differentiation of PTLD from ccRCC is clinically relevant. While the standard management of ccRCC is surgical excision, PTLD and other renal lymphomas are often treated by systemic chemotherapy without surgery. Although this is a single case description only, further studies of CEUS in renal masses may clarify the role of this emerging technique in guiding patient management. CEUS is particularly relevant in renal transplant patients due to the lack of nephrotoxicity.

TEACHING POINT

Post-transplant lymphoproliferative disorder (PTLD) can present as a focal renal mass in kidney transplant recipients. We describe one case of renal PTLD where the tumor was hypovascular throughout contrast enhanced ultrasound (CEUS) exam. The enhancement pattern of PTLD we observed in this case differed from the pattern typically seen in the main differential diagnosis, clear cell renal cell carcinoma (ccRCC).

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FIGURES

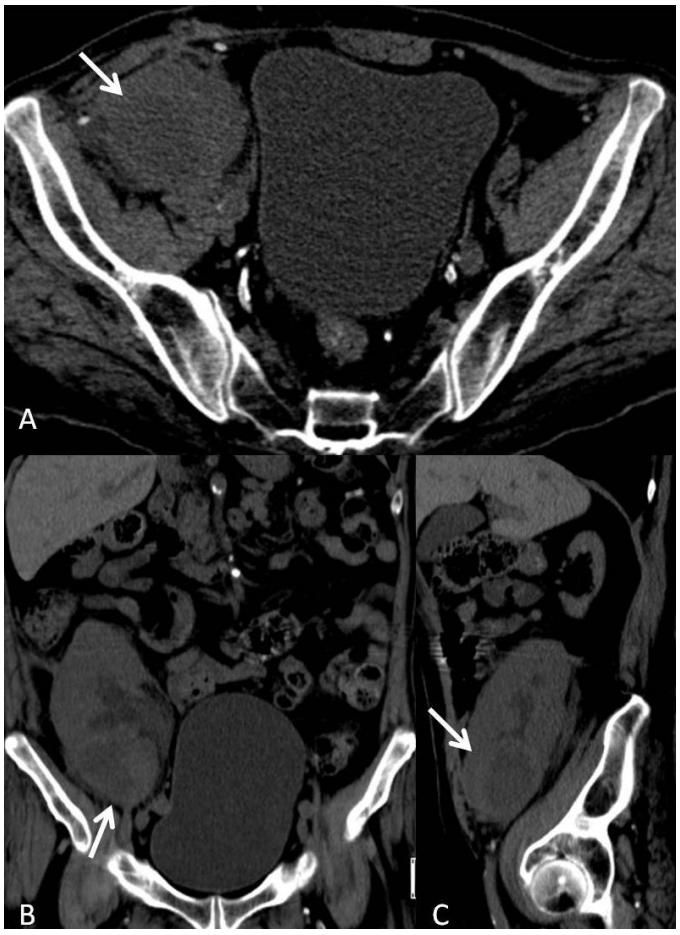


Figure 1: Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Axial (A), coronal (B), and sagittal (C) images show a round, centrally hypodense, 3 cm mass at the lower pole of the transplant kidney (arrow).
Technique: Noncontrast CT of the abdomen and pelvis (Scanner: Multidetector CT Siemens Sensation 16-slice®. Protocol: 212mAs, 120kV, 3mm slice thickness).

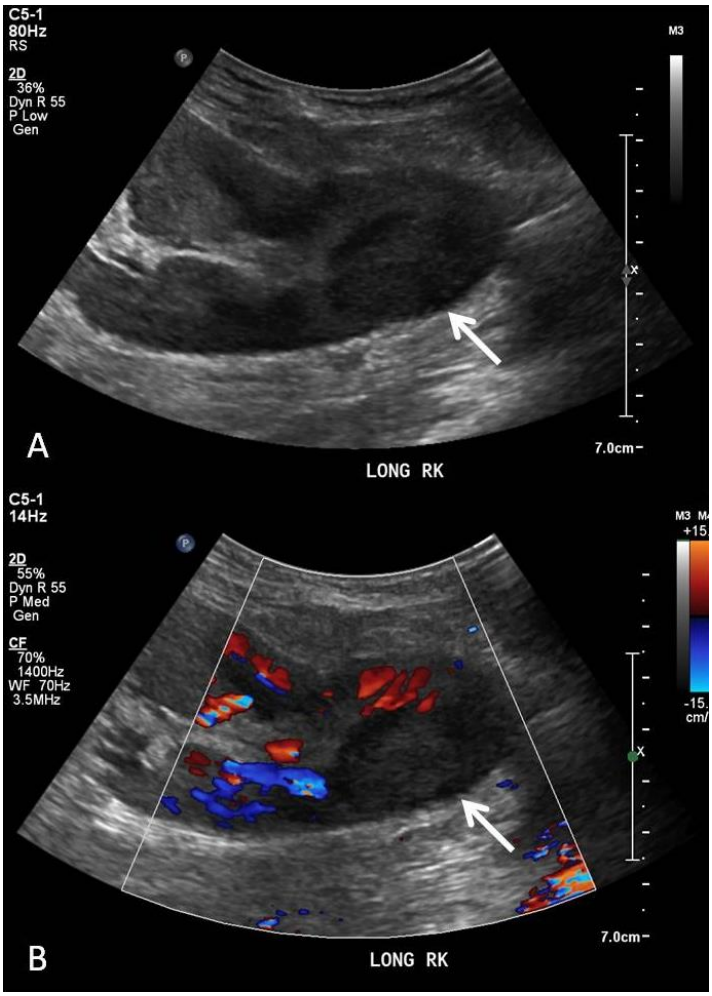
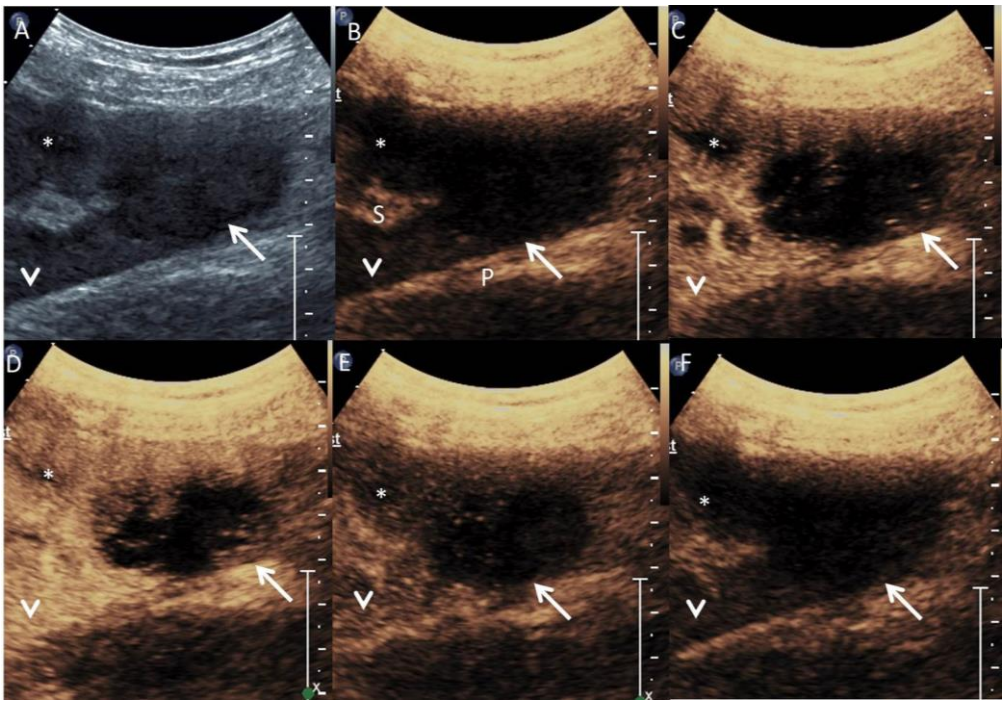


Figure 2 (left): Seventy-seven year-old man with post-transplant lymphoproliferative disorder. Findings: Longitudinal gray scale (A) and color Doppler (B) images demonstrate a solid, hypoechoic, hypovascular, cortically based mass (arrow) in the lower pole of the transplant kidney. Technique: Gray scale and color Doppler images of the right lower quadrant transplant kidney (Scanner: Phillips Epiq7®, curved probe, 1-5 MHz).

Figure 3 (bottom): Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Normal renal cortex (arrowhead), mass (arrow), and medullary pyramid (asterisk, *) are denoted on all images. Gray scale US (A) shows mass (arrow) in the lower pole transplant renal cortex. (B) Initial image from start of CEUS (0 seconds after injection) shows bright background echoes in the perinephric (P) and renal sinus (S) fat. The image is optimized to null renal signal, so renal cortex and mass are very hypoechoic. (C) Corticomedullary phase CEUS image (20 seconds) demonstrates early peripheral enhancement in the mass. Medullary pyramids hypoenhance in corticomedullary phase. (D) Parenchymal phase (also known as nephrographic, 30 seconds) CEUS image demonstrates progressive increase in peripheral enhancement in the mass, which remained persistently hypovascular to normal renal cortex throughout the exam. Medullary pyramid and cortex enhance similarly in this phase. (E) Delayed image (90 seconds) shows relative de-enhancement of kidney. Mass has minimal residual peripheral enhancement. (F) End of CEUS exam image (120 seconds) shows further de-enhancement, with appearance similar to (B), reflecting the minimal residual contrast in the blood pool at this time point. Note that the mass showed central non-enhancement, consistent with necrosis, throughout the CEUS exam.
Technique: Gray scale and contrast-enhanced ultrasound (CEUS) images of the right lower quadrant transplant kidney (Scanner: Phillips Epiq7®, curved probe, 1-5 MHz).



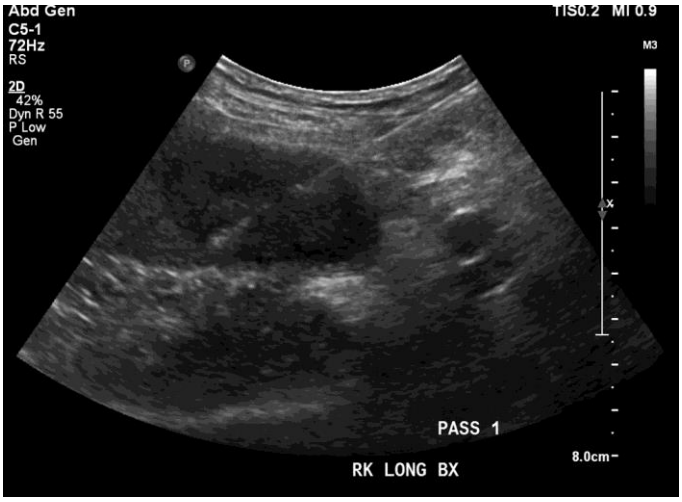


Figure 4: Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Gray scale image shows core biopsy needle in hypoechoic mass in lower pole of transplant kidney.
Technique: Ultrasound image of the right lower quadrant transplant kidney (Scanner: Phillips Epiq7®, curved probe, 1-5 MHz).

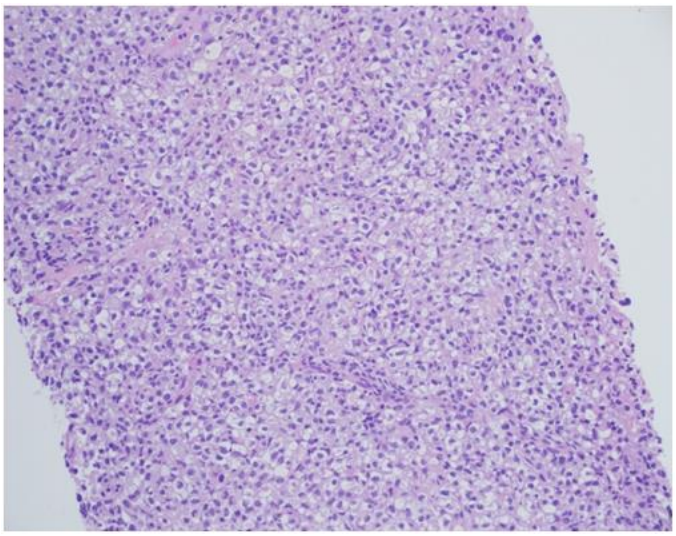


Figure 5: Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Tumor cells showed clear cytoplasm, which along with the sinusoidal vascular spaces, suggested clear cell renal cell carcinoma. No immunohistochemical stains were performed.
Technique: Hematoxylin and eosin (x200) stain of the core needle biopsy specimen.

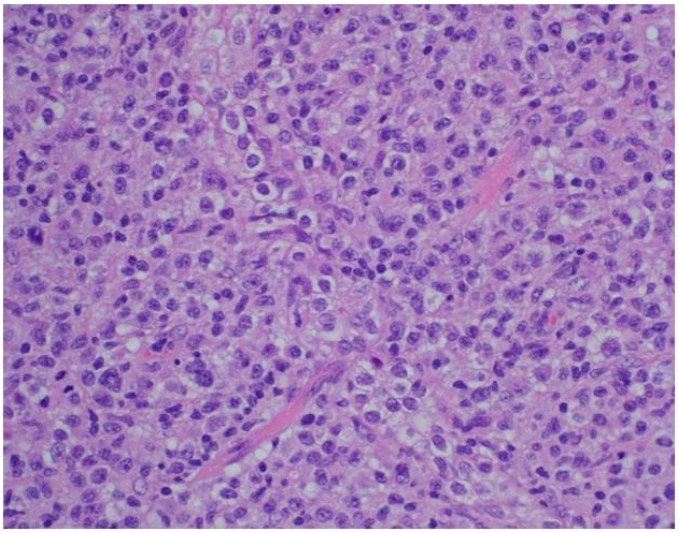


Figure 6: Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Tumor from the partial nephrectomy showing a diffuse growth pattern with a few cells showing cytoplasmic clearing.
Technique: Hematoxylin and eosin (x400) stain of the surgical partial nephrectomy specimen.

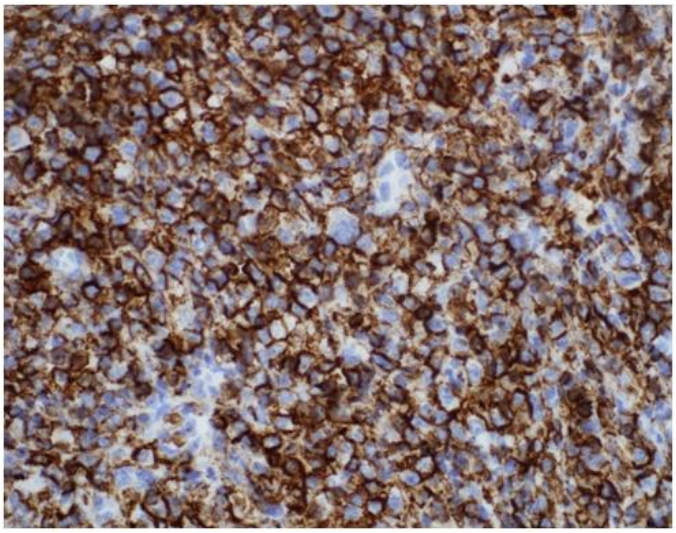


Figure 7: Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Tumor from partial nephrectomy showing diffuse positivity for CD 20.
Technique: High-power (x400) CD 20 immunohistochemical stain of the surgical partial nephrectomy specimen.

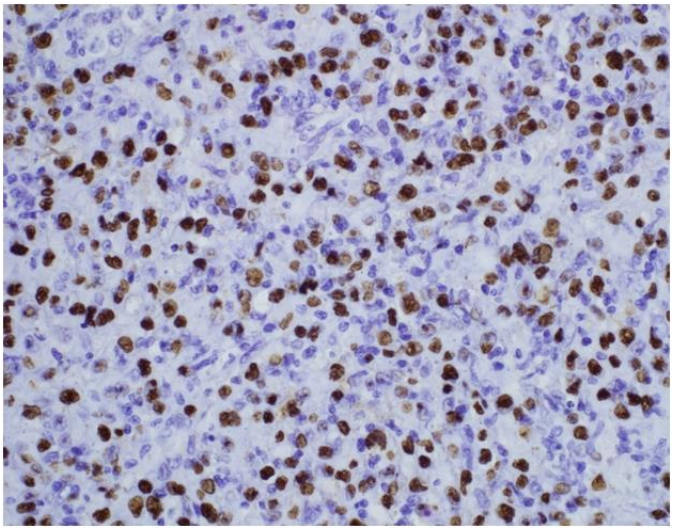


Figure 8 (left): Seventy-seven year-old man with post-transplant lymphoproliferative disorder.
Findings: Tumor cells show diffuse positivity for EBER by in situ hybridization.
Technique: High-power (x400) EBV-encoded RNA (EBER) stain of the surgical partial nephrectomy specimen.

Etiology	PTLD includes all lymphoid malignancies arising after transplantation
Incidence	1% of renal transplant recipients
Gender Ratio	Ratio 1.23:1 (M:F)
Age Predilection	Bimodal, young and older (<20, >50 years of age) age peaks
Risk factors	Epstein Barr virus (EBV) positivity
Treatment	Reduce immunosuppression, initiate chemotherapy
Prognosis	2 year overall survival of 70-83%
Findings on imaging	• After lymph nodes, renal allograft is second most common site of PTLD in renal transplant recipient • Presents as ill-defined or discrete renal mass • Lesions can be multiple, appear markedly hypoechoic (US), even cystic • When at renal hilum, can result in hydronephrosis • PTLD (and lymphoma) is hypovascular throughout contrast-enhanced exam (CT,MR, CEUS) • Hypovascularity differentiates PTLD from ccRCC, which is main differential diagnosis

Table 1: Summary table of key findings in post transplant lymphoproliferative disorder (PTLD) arising after renal transplantation.

Differential diagnosis	Grayscale US	CECT	MRI	CEUS
Post-transplant lymphoproliferative disorder (PTLD)	• Adenopathy, hilar mass, and resultant hydronephrosis have been described • This case: well-defined, discrete, hypoechoic, solitary renal mass	• Hypoenhances, hilar or cortical, single or multiple masses.	• T1 isointense, T2 hypointense • Minimal enhancement, similar to CECT	• This is first description • Enhancing, but hypovascular both in early (arterial) and later (parenchymal) phases • Hypovascularity is similar to enhancement with CECT/MR
Clear cell renal cell carcinoma (ccRCC)	• Small tumors often hyperechoic to renal cortex • Larger tumors hypoechoic or heterogeneous, exophytic, can have central anechoic necrosis	• Hyperenhances early (corticomedullary), hypoenhances late (nephrographic) • Necrosis, hemorrhage, and calcification common	• T1 isointense, T2 iso to hyperintense • Enhancement similar to CECT • Subtraction series may be useful to confirm enhancement	• Early, rapid (arterial phase) hyperenhancement relative to renal cortex • Later, hypoenhancement ("washout") on parenchymal phase • Similar to CT/MR • Perilesion rim-like enhancement ("pseudocapsule")
Angiomyolipoma	• Homogenously hyperechoic to renal cortex when small due to fat content • Lipid poor AMLs can be isoechoic • Heterogeneous when larger	• Measurable fat density is diagnostic • Heterogeneous, with fat, vessels, and soft tissue components when larger • High attenuation on NECT	• T1 hyperintense due to macroscopic fat • Macroscopic fat in mass follows subcutaneous fat • Vascular components enhance avidly • T2 hypointense	• Homogenous, hypoenhances to renal parenchyma • Persistent (greater delayed) enhancement compared with ccRCC

Table 2: Differential of solid renal masses in a transplant kidney with description of imaging findings.

ABBREVIATIONS

AML = Angiomyolipoma
CECT = contrast-enhanced computed tomography
CEUS = contrast-enhanced ultrasound
ccRCC = clear cell renal cell carcinoma
DLBCL = diffuse large B cell lymphoma
EBV = Epstein-Barr virus
FDG = fluorodeoxyglucose
MRI = magnetic resonance imaging
NECT = nonenhanced computed tomography
PET-CT = positron emission tomography-computed tomography
PTLD = post-transplant lymphoproliferative disorder
RCC = renal cell carcinoma
US = ultrasound

KEYWORDS

Contrast enhanced ultrasound; renal transplant; lymphoma; post-transplant lymphoproliferative disorder

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