

Original Article

Diagnosis of acute pyelonephritis by contrast-enhanced ultrasonography in kidney transplant patients

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Abstract

Background. Diagnostic imaging of acute pyelonephritis (APN) in renal transplanted patients is an important clinical issue. While conventional ultrasonography (US) has a limited diagnostic role, contrast-enhanced computer tomography and magnetic resonance imaging (MRI) represent the gold standard diagnostic tests. However, nephrotoxicity of either iodinated or paramagnetic contrast medium limits their use, especially in patients with kidney disease. Contrast-enhanced US (CEUS) may detect poorly perfused parenchymal renal areas, a useful feature in the diagnosis of APN. The aim of this study was to evaluate the diagnostic value of CEUS in APN compared with MRI as the reference test.

Methods. From a pool of 389 kidney transplant patients, we prospectively recruited 56 patients with clinical suspicion of APN of the transplanted kidney. They underwent both CEUS and MRI, performed in a blinded manner by two different operators. Sensitivity, specificity, accuracy, positive and negative predictive values, and K statistics were calculated.

Results. Thirty-seven out of 56 patients (66.1%) resulted positive for APN with the reference test, gadolinium-enhanced MRI. Thirty-five out of these 37 patients showed positive results for APN with CEUS, and 19 patients showed negative results for APN with both MRI and CEUS: sensitivity 95% (CI 82–99), specificity 100% (CI 83–100), accuracy 96% (CI 88–99), positive predictive value 100% (CI 90–100), negative predictive value 90% (CI 71–97) and K statistics 0.92 ($P < 0.01$).

Conclusions. Our results suggest, for the first time, the feasibility of CEUS, a low-cost and low-risk diagnostic procedure, in the diagnosis of APN in kidney transplant patients.

Keywords: acute pyelonephritis; cadence contrast pulse sequence; contrast-enhanced ultrasound; magnetic resonance; urinary tract infection

Introduction

Although significant advances have been made in surgical techniques and immunosuppression for renal transplantation, urinary tract infections remain a major problem, and acute pyelonephritis (APN) is a relevant cause of infectious complications in renal transplant recipients. Recently, a remarkable cumulative incidence of APN of 19–23% has been described [1,2]. APN, facilitated by immunosuppression and urological procedures after kidney transplantation, is a possible independent risk factor for deterioration of graft function [3,4]. APN of a transplanted kidney should be suspected in the case of unexplained fever, leucocytosis, leucocyturia and high levels of C-reactive protein. However, this approach fails to differentiate between pyelitis and pyelonephritis, an important clinical distinction because only the latter involves damage to the kidney parenchyma, carrying a risk for kidney scarring [5]. The gold standard for APN diagnosis in routine clinical practice is contrast-enhanced computer tomography (CT), despite its high-dose radiation, contrast media nephrotoxicity risk and a high economic cost. In patients with failure of the renal allograft, magnetic resonance imaging (MRI), rather than CT examination, is increasingly used [6,7]. Conventional ultrasonography (US) has a marginal role in this clinical scenario because of a low specificity, failing to identify APN lesions in up to 50% of patients, and second-line techniques are therefore required to detect parenchymal lesions. US can only detect focal, poorly marginated hypo- or occasionally hyperechoic areas, caused by interstitial oedema and/or haemorrhage [8]. Doppler US (DUS) has an improved sensitivity in detecting parenchymal abnormalities, as most pyelonephritic lesions are ischaemic. These are better identified by power Doppler US than by colour Doppler US [8]. Thus, power Doppler US has been considered as a possible alternative imaging technique, but unfortunately, it is limited in the detection of low flow, and also normal flow in small vessels, and might therefore miss renal parenchymal changes in APN [9].

Table 1. Patient characteristics

Number of patients	56
Age at transplantation (years), mean \pm SD	47.2 \pm 9.1
Age at the examination (years), mean \pm SD	50.1 \pm 9.1
Male/female, <i>n</i> (%)	25/31 (45%/55%)
Diabetes, <i>n</i> (%)	18 (32%)
Body mass index (kg/m ²), mean \pm SD	23.8 \pm 2.7
eGFR (mL/min/1.73 m ²), mean \pm SD	32.3 \pm 9.2
APN with gadolinium-enhanced MRI, <i>n</i> (%)	37 (66.1%)
APN with contrast-enhanced US, <i>n</i> (%)	35 (62.5%)

The advent of newer US contrast agents has helped to better detect areas of poor renal parenchymal perfusion. Contrast-enhanced US (CEUS) can improve the detection of low flow by improving the signal-to-noise ratio, and can improve the sensitivity of US in the clinical setting of APN [10]. Nonetheless, early preliminary reports of CEUS showed a lower sensitivity than contrast-enhanced CT for evaluating APN in native kidneys [11]. Cadence contrast pulse-sequence (CPS) imaging is one of the newest sensitive methods of US, based on the characteristics of non-linear bubble behaviour. This technique constructs images by transmitting a series of pulses with different amplitudes and phases, enabling the distinction between non-linear signals reflected by the contrast agent and linear responses of the tissue. This makes simultaneous viewing of tissue only and contrast-only images possible, as described in detail by Phillips and Gardner [12]. Thus, a new diagnostic test with a better risk/benefit profile in terms of accuracy, safety and cost is now available. In this study, we prospectively explored the diagnostic power of CEUS in the diagnosis of APN in kidney transplant patients, compared with gadolinium-enhanced MRI, considered as the reference tool.

Materials and methods

We considered patients admitted to our unit with a clinical diagnosis of APN, who underwent both CEUS and gadolinium-enhanced MRI. The

two diagnostic techniques were performed in a blinded manner by two different operators after informed consent was obtained. MRI was performed after CEUS. We used a Sequoia 512 US unit (Acuson–Siemens, Mountain View, CA, USA) with a 6C2 probe for the US detection of renal parenchymal changes, including the Cadence™ CPS technology, which is a low mechanical-index (MI) technique with a transmission frequency of 2.0 MHz. We injected a 2.4-mL bolus of the US contrast agent sulphur hexafluoride (SonoVue™, Bracco, Milan, Italy) flushed with 10 mL of normal saline solution. Triangular areas of decreased perfusion visible on both longitudinal and axial scans were considered indicative of APN [13]. The CPS scanning was done at low output power (MI = 0.2). To depict the wash-in/wash-out characteristics, at the peak of the enhancement, a short period of high output power (MI >1) was used to destroy all the bubbles in the scanning field. After such a period, there was visible replenishment of bubbles from outside the field by a new wash-in of bubbles. This manoeuvre enabled repeated evaluations of temporal patterns of enhancement. In addition, all patients underwent MRI examination (Achieva 1.5T, gradient 30 mT, Philips, Best, the Netherlands), performed within 12 h after the CEUS studies had been completed, using 10 mL of i.v. gadobenate dimeglumine (Multihance™ 0.5 M, Bracco, Milan, Italy) contrast agent (flow 1 mL/s), with a slice thickness of 2 mm. Areas of decreased attenuation of the renal parenchyma visible immediately after contrast injection, or areas of increased attenuation on the delayed scans, were considered indicative of APN.

Statistical analysis

The CEUS and MRI findings were compared, using the result of gadolinium-enhanced MRI as the ‘gold standard’. The sensitivity, specificity and accuracy with 95 confidence intervals in the diagnosis of APN by CEUS in kidney transplanted patients were calculated. Positive and negative predictive values (PPV and NPV) were also evaluated. Kappa statistic was used to evaluate the agreement between the two diagnostic techniques. A value of Kappa statistic of 1 indicates perfect agreement, while a zero value indicates that the presence/absence of the disease assignment can be considered random. Logistic regression was used to explore the possible predictive power in the diagnosis of APN of some clinical (gender, age, transplantation vintage, diabetic status and body mass index) and laboratory variables (eGFR by MDRD four-variable formula). All statistical analyses were performed using SPSS for Windows version 17.02.

Results

Between September 2008 and November 2009, 56 patients (25 male and 31 female, 18 diabetics) were prospectively

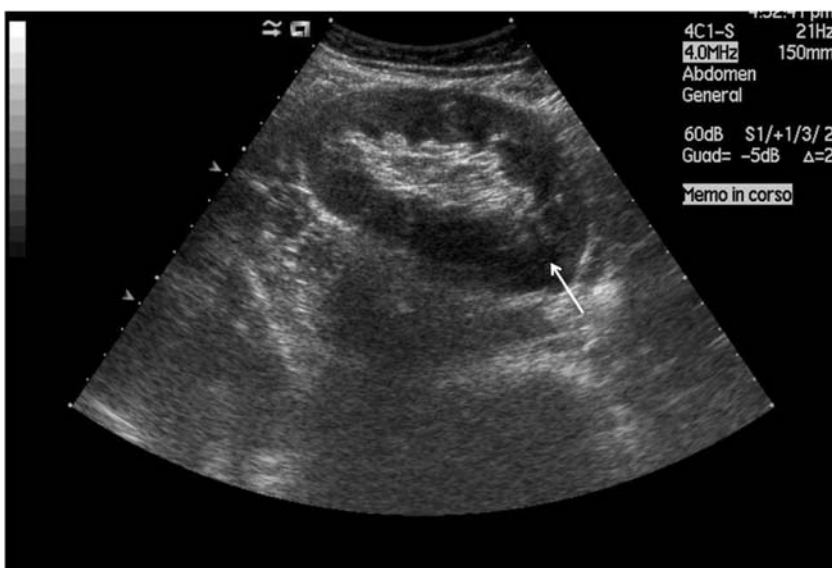


Fig. 1. Ultrasound imaging findings of a transplanted kidney in a 30-year-old man with dysuria and fever; longitudinal US scan has not shown clear signs of acute pyelonephritis.

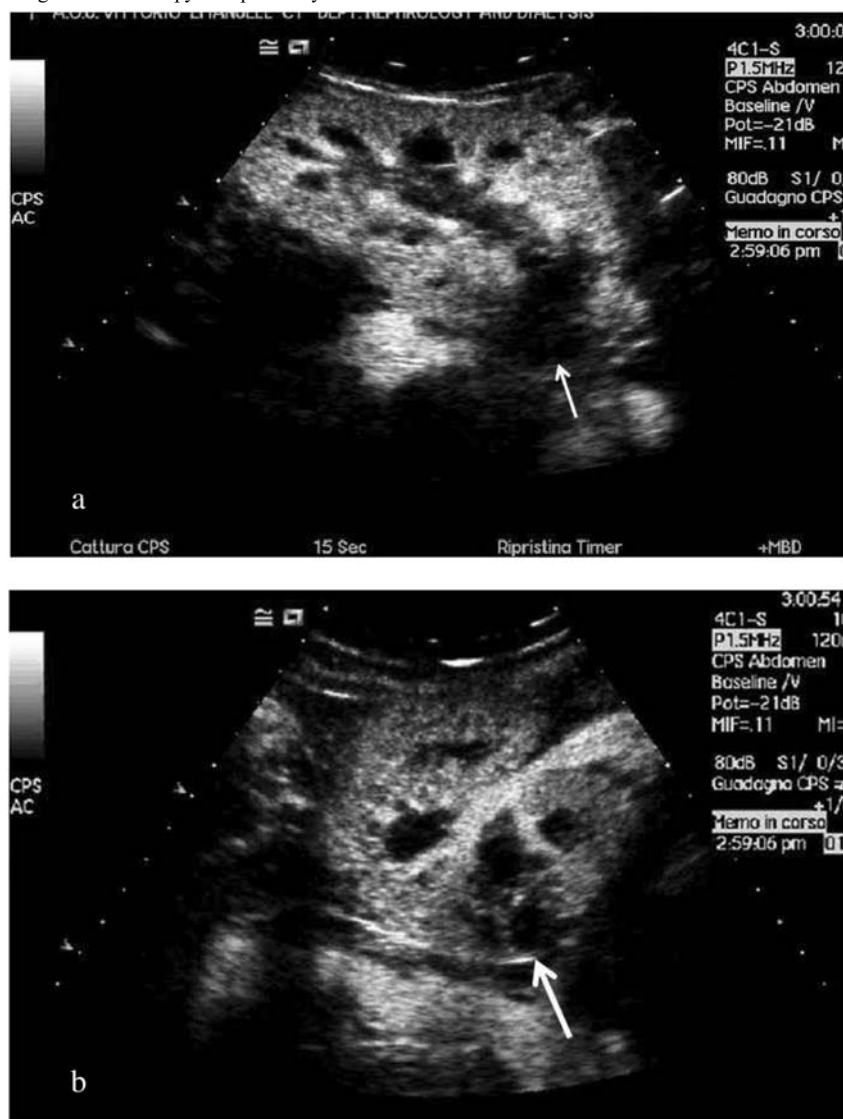


Fig. 2. CEUS obtained 36 s after contrast injection detects a clear, wedge-shaped area (white arrow) of hypoperfusion due to acute pyelonephritis. a, Longitudinal scan; b, axial scan.

recruited in the study from a pool of 389 transplanted patients from two departments. Characteristics of patients are reported in Table 1. Renal function was reduced, with an estimated eGFR of 32.3 ± 9.2 mL/min/1.73 m². Thirty-seven out of 56 patients (66.1%) showed positive results for APN at the gadolinium-enhanced MRI, considered the gold standard diagnostic tool.

Thirty-five out of these 37 patients were considered as having an APN with the CEUS diagnostic tool (sensitivity of 95%, 95% CIs 82–99%) showing evident hypoechoic, hypoperfused areas. Characteristic imaging of a representative case of APN in a kidney transplant patients is represented in Figures 1 and 2 (plain US and CEUS) and Figure 3 (MRI).

All 19 negative patients at gadolinium-enhanced MRI were also negative at CEUS examination (specificity of 100%), but the lower limit of 95% CI of specificity was 83%, given the small sample size. Diagnostic accu-

acy was 96% (95% CIs 88–99). Whereas the positive predictive value was high (100%, 95% CIs 90–100), indicating a good performance when the result of CEUS is positive, the negative predictive value was only 90% (95% CI 71–97), indicating a relevant uncertainty in excluding disease in the case of negative CEUS test. All these performance diagnostic parameters are shown in Table 2.

In two patients (one male diabetic patient and one female non-diabetic patient), the CEUS technique was unable to detect the APN found with gadolinium-enhanced MRI. As a consequence, the results of the K statistics were equal to 0.92 ($P < 0.01$), indicating a non-random association between the two diagnostic techniques.

Logistic regression was not able to select any covariates as predictors associated to APN, such as gender, age, body mass index, estimated GFR, transplantation vintage and diabetic status.

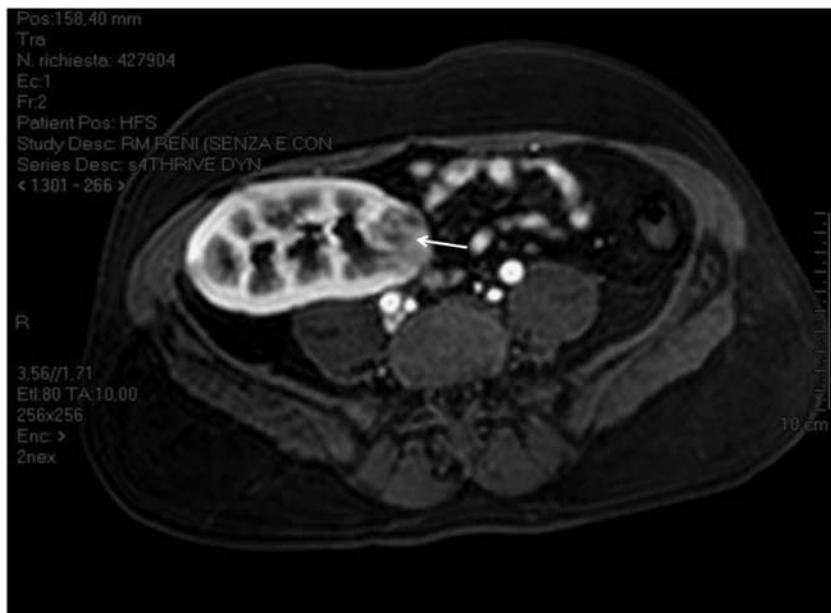


Fig. 3. Gadolinium-enhanced MRI of acute pyelonephritis in the same transplant kidney (arrow).

Discussion

This is the first report focused on the availability of CEUS, a new diagnostic tool of APN in kidney transplant patients. We believe that it may become the first-line diagnostic tool in this area because of its low cost and low toxicity, combined with a good diagnostic performance in terms of sensitivity, specificity, accuracy and positive predictive value.

It is of note that APN is rare in native kidneys, and it should always be considered in any kidney transplant patient with fever, derangement of kidney function, and laboratory signs of systemic (acute increase of C-reactive protein) and urinary (leucocyturia) inflammation [14]. APN in kidney transplant is favoured by immunosuppression [4] and by the frequent alterations of urine flow from the transplanted kidney towards the bladder, such as urostenosis and insufficiency of the neo-ureter–bladder junction [14]. The specific finding useful for the differential diagnosis between APN and the clinically less relevant pyelitis is the presence of ischaemic parenchymal lesions seen as

triangular hypoechoic, hypoperfused areas of medulla at the CEUS test [11–16] (Figure 2a and b). Areas of hypoperfusion could also occur in acute rejection; however, in this case, we would expect a ‘diffuse pattern’ compared to focal hypoperfused areas with a ‘triangular shape’ in the case of APN. Unfortunately, this issue is not specifically investigated in our study, given that patients with acute rejection were not included.

It is now clear that diagnosis of APN requires a technique able to study the microcirculation of kidney parenchyma, a level that cannot be reached by conventional colour and power Doppler US [17]. On the other hand, the gold standard techniques, contrast-enhanced CT and MRI, carry the risk of nephrotoxicity, especially in patients with deranged kidney function [18]. Their role for diagnosis and, even more, for monitoring during follow-up is therefore questionable [17–19].

This study has some pitfalls and limitations. The specificity of CEUS in the diagnosis of APN suggested by this study is very high (100%), but it is based on few cases (19 patients). Strict selection criteria were adopted to perform the CEUS examination, which translated into a high pre-test probability of APN in the transplanted kidney. Notably, in such cases, performance of the diagnostic test is increased by increasing the pre-test probability of the disease (37 out of 56 patients, 66% in this study) (Table 1). Due to the small sample size of patients without APN, the lower limit of the 95% confidence interval [20] of the specificity is only 83%, although with a point estimate of 100%, indicating that some uncertainty is present around the high point estimate. Similarly, the negative predictive value of 90% indicates that a relevant uncertainty remained in excluding disease in the case of negative CEUS test especially when considering the lower confidence limit (71%). Also, sensibility of the CEUS test is not very high (95%), especially when considering the lower confidence limit (82%) indicating that, with a conservative approach, ~20% of patients with APN could not be diagnosed with CEUS.

Table 2. Diagnostic performance of CEUS in the diagnosis of APN of transplanted kidney, using MRI as reference

		APN by MRI (reference)		
		Positive	Negative	Total
APN by CEUS (test)	Positive	35	0	35
	Negative	2	19	21
	Total	37	19	56
Parameter	Estimate (%)	95% CIs		
Sensitivity	95	82–99		
Specificity	100	82–100		
Diagnostic accuracy	96	87–100		
Positive predictive value	100	90–100		
Negative predictive value	91	70–99		

In any case, our results also have several strengths, such as their originality, very important clinical and therapeutic implications, the low cost of the CEUS procedure with a very low risk of toxicity, and some technical facilitation derived from the superficial location of the transplanted kidney. An accurate diagnosis of APN has very important clinical and therapeutic implications, indicating the need of a more prolonged and targeted antibiotic therapy when compared with the more simple 'pyelitis' and, thereafter, on the possible solution of the underlying urological problem [19]. Regarding the latter point, it is of note that a rapid enhancement and de-enhancement of the kidney can sometimes create difficulties in adequate image interpretation [19,21]. For obvious reasons, it is not possible to have a simultaneous comparison of two kidneys during CEUS, but contrast injection can be repeated for unclear cases [21,22]. Current harmonic software programs produce a significant loss in spatial resolution and image quality [22]. However, for its superficial site, the transplanted kidney is easy to study, not having the problems of assessing deep regions throughout intestinal air, typical of native kidneys especially in obese patients. Another limitation of CEUS, compared with MRI, is dependence from the operator's skill. In fact, CEUS is usually performed routinely by a limited number of experienced operators. In our opinion, evaluation of renal parenchyma to check for acute pyelonephritis is not technically difficult, and in this study, we found a very good inter-reader agreement in diagnosis (K statistic = 0.92, $P < 0.001$). Nevertheless, this might limit reproducibility of our results.

In conclusion, our data suggest, for the first time, the feasibility of CEUS in the diagnosis of APN in kidney transplant patients. Our results are promising also in light of the low risk and low cost of this diagnostic procedure. Future studies with a larger series of patients and with various abnormalities including acute rejection are needed in order to confirm the primary role of CEUS in diagnosis and follow-up of APN of transplanted kidney.

Conflict of interest statement. None declared.

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