

### Contrast-enhanced ultrasonography with microbubbles for successful screening of kidney tumours

Sir,

A 70-year-old female had developed chronic kidney disease (CKD) stage 5 due to autosomal dominant polycystic kidney disease (ADPKD), for which she performed peritoneal dialysis for 1 year until her kidney transplantation.

On clinical evaluation, the patient mentioned a weight loss of 2 kg in the last 6 months but with normal appetite and without asthenia. Medical examination revealed the absence of fever and no lymphadenopathies. The polycystic liver and both native polycystic kidneys were enlarged on abdominal palpation, but with no obvious change in volume versus previous check-ups. The chest X-ray, cardiac echography and dermatological and gynaecological examinations were normal.

The abdominal ultrasonography revealed nodular lesions in both native polycystic kidneys, which had not been visualized before, of 1.4 cm diameter in the right and 2 cm diameter in the left kidney. Colour Doppler and power Doppler could not demonstrate arterial flow in these nodules. However, a contrast-enhanced ultrasonography (CEUS) with the use of Sono-Vue<sup>®</sup> (BR1, Bracco, Milan, Italy), a contrast agent generating microbubbles by mixing with saline solution, showed vascularization in both lesions, suggesting solid vascularized tumours (Figure 1). Ultrasound-guided fine needle punctures of both lesions were performed. The cytology of the suspected mass in the right kidney was considered normal. The puncture of the left nodular lesion revealed papillary cells with nuclear atypia, suggesting a neoplasm.

Shortly thereafter, a surgical resection of the left kidney was performed. Histopathology confirmed the diagnosis of polycystic kidney disease with the presence of a subcapsular nodule, revealing a renal cell carcinoma (RCC), Fuhrman grade 3. Further staging with head and chest CT scan, bone scintigraphy and contrast-enhanced abdominal CT scan did not demonstrate metastases. The RCC was staged as a pT1a/N0/M0, compatible with stage 1 disease. The post-operative follow-up was uneventful, and a 36-month post-operative check-up excluded tumour relapse.

RCC is an infrequent complication of ADPKD. An increased incidence as compared to the general population has not clearly been demonstrated, but the disease seems to have different and more aggressive characteristics in ADPKD [1].

In general, diagnosing RCC in ADPKD is difficult and often delayed, partially because of the cystic nature of ADPKD itself. Moreover, typical symptoms for RCC such as fever, flank pain and haematuria are frequently observed in ADPKD due to other complications, like lithiasis, mass effect, cyst bleeding or cyst infection [1]. The patient in the presented case did not have any complaints or clinical aberrations, except for a moderate weight loss. The diagnosis was suspected on an ultrasound examination, confirmed by



**Fig. 1.** Contrast-enhanced sonography after intravenous injection of 2.4 mL Sono-Vue<sup>®</sup> in the arterial phase: the hyperechoic spots correspond to Sono-Vue<sup>®</sup> bubbles in vessels within the nodule and around the cyst (arrows).

CEUS and histologically proven after an ultrasound-guided puncture.

In complicated cystic renal lesions, the most important clue in differentiation between benign and malignant cysts is the presence or absence of contrast enhancement with CT or MR imaging. Although ultrasonography can easily demonstrate fine septation, irregular wall thickening or the presence of a small mural nodule, its role has been limited owing to the inability to provide contrast enhancement. This major drawback is being overcome by recent advances in Doppler technology and the introduction of sonographic contrast agents [2].

CEUS can easily differentiate cystic lesions from solid lesions and suggests a solid tumour when showing hypervascularization [2]. It was demonstrated that CEUS allowed the most optimal visualization of tumour vascularization and a high diagnostic accuracy in differentiating between benign and malignant cystic lesions, compared with contrast-enhanced CT scan and MRI. CEUS showed 100% positive predictive value for benign cysts. Also a higher negative predictive value was demonstrated for CEUS, pointing out that patients could be spared additional CT-scanning or MRI [2].

CEUS is a valuable and safe alternative in the case of contra-indication for contrast-enhanced CT scan or MRI with gadolinium. Ultrasonographic contrast agents exhibit an excellent safety profile with no specific hepatic, renal or cerebral toxicity. No allergic reactions have been reported [3]. The iodine-containing contrast used for CT scan is deleterious in the case of contrast allergy, hyperthyroidism or risk of contrast nephropathy [4]. Because of the use of ionizing radiation, CT scan increases the risk for developing cancer. MRI is contra-indicated in patients having a pacemaker or internal defibrillator. In patients with renal failure, the contrast agent used during MR imaging, gadolinium, was recently associated with nephrogenic systemic fibrosis (NSF), a serious and irreversible disease characterized by a painful thickened skin [5]. The United States Food and Drug Administration (FDA) advises avoidance of gadolinium in patients with advanced renal failure (GFR <15 mL/min)

and prudence in the case of moderate renal failure (GFR <30 mL/min). All these drawbacks can be obviated by the performance of CEUS, an interesting option especially in patients with CKD.

In conclusion, CEUS is a valuable, safe and easy tool in the diagnosis of vascularized lesions, such as kidney tumours in ADPKD patients.

*Conflict of interest statement.* None declared.

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## Nocturnal hypoxia is associated with elevated C-reactive protein in dialysis patients

Sir,

Sleep apnoea syndrome (SAS), characterized by repetitive nocturnal hypoxia, is a risk factor for cardiovascular disease (CVD) [1]. In addition, dialysis patients have a high prevalence of SAS (20–50%) in comparison to the general population (2–4%) [2]. The purpose of this study was to investigate the relationship between plasma C-reactive protein (CRP), an independent risk factor for CVD [3], and nocturnal hypoxia in dialysis patients.

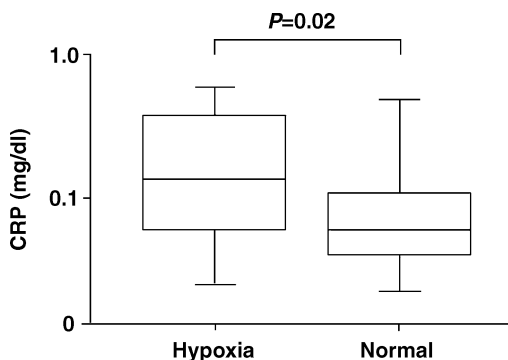
This study followed 88 maintenance haemodialysis patients (male: 53.4%, age: 64.2 ± 24.5 years, BMI: 22.3 ± 9.1, duration of dialysis: 4.7 ± 4.4 years, diabetes mellitus: 39.8%) in Koga Red Cross Hospital, who underwent the overnight pulse oximetry (PULSOX-M24, Teijin Pharma Ltd, Japan) on dialysis day. In addition, blood tests including plasma CRP levels were measured. Plasma CRP was deter-

**Table 1.** Clinical characteristics of the study population

Characteristics	Hypoxia (n = 29)	Normal (n = 59)	P-value
Age (years)	68.4 ± 10.1	62.1 ± 13.1	0.02
Man, n (%)	19 (65.5)	28 (47.5)	0.11
BMI (kg/m <sup>2</sup> )	22.5 ± 6.9	21.8 ± 4.4	0.60
Diabetes mellitus, n (%)	11 (37.9)	24 (40.7)	0.80
Duration of dialysis (years)	3.9 ± 3.4	5.1 ± 4.7	0.20
Kt/V	1.1 ± 0.4	1.3 ± 0.3	0.03
Intra-dialytic weight gain (%)	3.2 ± 1.6	3.6 ± 1.8	0.32
Cardiothoracic ratio (%)	52.7 ± 5.9	49.7 ± 5.0	0.02
ANP (pg/ml)	61.1 ± 63.9	64.6 ± 64.1	0.85
Systolic blood pressure (mmHg)	158.4 ± 20.7	155.0 ± 19.9	0.45
WBC (10 <sup>3</sup> /μl)	5.6 ± 1.5	5.4 ± 1.6	0.67
Haemoglobin (g/dl)	9.0 ± 1.7	9.6 ± 1.4	0.07
Serum albumin (g/dl)	3.6 ± 0.5	3.7 ± 0.5	0.46
3% ODI (events/h)	10.6 ± 10.9	4.6 ± 4.8	0.01
Epworth Sleepiness Scale	6.1 ± 4.2	5.0 ± 4.1	0.23

ANP, atrial natriuretic peptide; ODI, oxygen desaturation index; BMI, body mass index.

Values expressed as mean ± SD or number (percent).



**Fig. 1.** Comparison of plasma CRP between hypoxia and normal groups.

mined using the latex agglutination assay (Pureauto S CRP latex, Daiichi Pure Chemicals, Japan). Patients with systemic inflammatory disease, active malignancy, pulmonary disease and symptomatic heart failure were excluded. The patients with average SaO<sub>2</sub> ≤96% by pulse oximetry were defined as the hypoxia group, and others were defined as the normal group.

Twenty-nine patients (33.0%) were classified into the hypoxia group. Age (68.4 versus 62.1 years, *P* = 0.02), cardiothoracic ratio (CTR) (52.7 versus 49.7%, *P* = 0.02), 3% oxygen desaturation index (ODI) (10.6 versus 4.6/h, *P* = 0.01) and plasma CRP (0.26 versus 0.14 mg/dl, *P* = 0.02) were significantly higher in the hypoxia group than in the normal group (Table 1, Figure 1). On the other hand, Kt/V (1.1 versus 1.3, *P* = 0.03) was significantly lower in the hypoxia group than in the normal group (Table 1). After adjusting for age, BMI, diabetes, Kt/V, CTR, systolic blood pressure, haemoglobin and serum albumin in a logistic regression analysis, nocturnal hypoxia was independently associated with elevated CRP (odds ratio 4.88; 95% confidence interval 1.16–20.60; *P* = 0.03).