Clinical Kidney Journal, 2017, vol. 10, no. 5, 655–660

doi: 10.1093/ckj/sfx041
Advance Access Publication Date: 12 June 2017
Original Article

ORIGINAL ARTICLE

Usefulness of ^{99m}Tc-dimercaptosuccinic acid renal scan in the diagnosis and follow-up of acute tubulointerstitial nephritis in children

Enrico Vidal[1], Elisabetta Miorin[2], Pietro Zucchetta[3], Elisa Benetti[1], Germana Longo[1], Davide Meneghesso[1], Mattia Parolin[1] and Luisa Murer[1]

[1]Nephrology, Dialysis and Transplant Unit, Department of Women's and Children's Health, University-Hospital of Padova, Padova, Italy, [2]Pediatric Clinic, DPMSC, University-Hospital of Udine, Udine, Italy and [3]Department of Nuclear Medicine, University-Hospital of Padova, Padova, Italy

Correspondence and offprint requests to: Enrico Vidal; E-mail: enrico.vidal@inwind.it

Abstract

Background: Symptoms and signs of acute tubulointerstitial nephritis (ATIN) are nonspecific; therefore, renal biopsy is often necessary to clarify the diagnosis. The aim of this study was to evaluate the use of ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy in the diagnosis and follow-up of ATIN.

Methods: We retrospectively reviewed the charts of five patients (nine renal units) with a median age of 14 years who underwent DMSA scan after a clinical and/or biopsy-proven diagnosis of ATIN. The exam was performed within 1 month after disease onset and repeated at a median time of 12 months after the acute phase.

Results: DMSA renal scans performed during the acute phase allowed the discovery of suggestive findings, including diffuse reduction of the renal uptake of radionuclide and presence of multiple 'cold' focal lesions in a corticomedullary distribution. The follow-up scintigraphy resulted normal in two patients who were treated with steroids and in one patient who presented a mild renal dysfunction in the acute phase. By contrast, the control scan showed persistent renal damage in one patient who was further readmitted because of hypertension and in one renal transplanted patient who presented a Stage 3 acute kidney injury in the acute phase.

Conclusions: DMSA renal scan might be a reliable tool for an early non-invasive diagnosis of ATIN in children and might be particularly useful in those patients who are not candidates for a kidney biopsy. Moreover, DMSA scan gives accurate follow-up evaluation, as it allows monitoring of the evolution of acute renal parenchymal inflammation with potential risk of renal scar formation. Due to the small sample size, our findings warrant further validation in a larger study.

Key words: acute kidney injury, acute tubulointerstitial nephritis, children, DMSA scan, renal scar

Received: June 9, 2016. **Editorial decision:** March 30, 2017

Clinical Kidney Journal
ckj

Introduction

Acute tubulointerstitial nephritis (ATIN) is an important cause of acute kidney injury (AKI) in children and it accounts for up to 7% of kidney biopsies performed to investigate unexplained causes of AKI [1–3]. Upon histological examination, the disease is characterized by interstitial inflammatory infiltrate associated with acute tubular epithelial lesions. Patients usually present nonspecific signs and symptoms of acute renal dysfunction; therefore, the diagnosis is often delayed or represents a challenge for clinicians and renal biopsy becomes necessary. ATIN can be initiated by medications and infections, and can be the result of an immune-mediated disease or be associated with uveitis in the context of tubulointerstitial nephritis with uveitis (TINU) syndrome. However, a significant proportion of cases remain without specific aetiology, further complicating the overall management. Early recognition and adequate therapy usually lead to an excellent prognosis [4].

A number of laboratory tests and exams have been proposed as possible diagnostic tools for ATIN. Eosinophilia and eosinophiluria have been associated with ATIN [5, 6]; however, these both performed poorly in distinguishing ATIN from other causes of AKI, and these demonstrated only moderate sensitivity [6, 7]. Gallium-67 (Ga-67) scintigraphy has been suggested as a useful non-invasive method in patients with a clinical suspicion of ATIN [8–11]. However, its diagnostic performance and usefulness remain controversial [12]. Moreover, this exam is aggravated by a significant biological cost due to the high radiation exposure, especially in childhood.

To the best of our knowledge, no previous studies have explored the role of ^{99m}Tc-dimercaptosuccinic acid (DMSA) renal scan in the diagnosis and follow-up of ATIN. This scintigraphy is accessible in most paediatric nephrology units and it is easily obtained at a lower biological cost. By using the dose recommendations of the European Pediatric Task Group [13], the radiation dose for DMSA scintigraphy has been estimated as 1 mSv regardless of the child's age, a burden that is significantly lower than that associated with Ga-67 scintigraphy [14].

We retrospectively reviewed five cases of ATIN evaluated in our Unit to investigate the potential usefulness of DSMA renal scan in the diagnosis and follow-up of histologically confirmed ATIN. We focused on each scintigraphic pattern to identify peculiar findings and their correlation with histological data.

Materials and methods

We describe five patients (nine renal units) with ATIN who were admitted to the Pediatric Nephrology Unit at the University-Hospital of Padova, Italy, from January 2006 to December 2014. Diagnosis of ATIN was biopsy-proven in four out of five patients, whereas one patient fulfilled the diagnostic criteria of TINU syndrome.

In all patients, a first DMSA renal scintigraphy was performed in the acute phase, within 1 month of disease onset. Moreover, all patients underwent a control scan at least 6 months after the ATIN diagnosis. Images were obtained by means of a gamma camera equipped with a high-resolution collimator after an intravenous injection of ^{99m}Tc DMSA, according to the European Association of Nuclear Medicine guidelines [15]. About 3–4 h after injection with the tracer, one posterior, one anterior and two posterior oblique images of the kidneys were acquired. The fractional left and right renal activities were calculated for each kidney. Renal scintigraphic patterns were independently interpreted by one senior nuclear-medicine physician who was blinded to the clinical status of the patient (acute DMSA scan).

A data sheet was designed to record demographic information, clinical symptoms, laboratory results including complete urinalysis and blood cell count, blood urea nitrogen, serum creatinine and electrolytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulins, C3, C4, antinuclear-antibodies, extended viral and bacterial serologies, and renal ultrasound US and DMSA renal scan results. Estimated glomerular filtration rate (eGFR) was calculated by using the updated Schwartz formula (eGFR = 0.413 × height/serum creatinine) [16]. The data sheet was completed based on the information in the patient records.

Results

Case descriptions

The median age of patients at ATIN diagnosis was 14 years (range 3–17). Past medical history was unremarkable in four cases, whereas one patient (Case 5) received a renal transplantation 2 years before, because of chronic renal failure of unknown origin. His renal function before the onset of ATIN was normal (eGFR of 115 mL/min/1.73 m^2), as were surveillance protocol kidney biopsies performed at 6 and 12 months after transplantation (Class 1 based on Banff classification).

All patients experienced a similar pattern of nonspecific symptoms at admission, such as fever, fatigue, arthralgias, anorexia and weight loss. Polyuria was reported in three patients, whereas daily urinary output was normal in the remaining two cases. The transplanted patient (Case 5) was also admitted with a 2-day history of macroscopic haematuria. Table 1 reports patient laboratory data at ATIN presentation.

In Case 5, serological testing and positive reverse transcription-polymerase chain reaction (RT-PCR) performed on both blood and renal tissue confirmed an acute adenovirus infection. In all other patients, cultures and serological testing, as well as autoantibodies and complement factors dosages, resulted negative. Previous medical history was non-significant, especially as far as medication exposure was concerned. Renal ultrasound demonstrated enlarged hyperechoic kidneys in Cases 1, 2 and 4, whereas no abnormalities were found in the other patients. One month after the onset of ATIN, Case 4 was readmitted because of bilateral eye pain, accompanied by photophobia. An ophthalmological evaluation showed clinical findings of bilateral anterior acute uveitis, thus allowing the diagnosis of TINU syndrome. In this patient, renal biopsy was not performed because of the ocular findings and the progressive clinical improvement, with restoration of a normal renal function within 6 weeks.

In the other four patients (Cases 1, 2, 3 and 5), renal biopsy was performed after a median time of 5 weeks (range 4–7) and there was a median eGFR of 57 mL/min/1.73 m^2 (range 32–80). Common findings included patchy infiltration of inflammatory cells within the renal interstitium with associated oedema, sparing the glomeruli and blood vessels (Figure 1). Tubules presented variable focal lesions, including loss of the brush border and presence of regenerative changes (Figure 2).

All patients experienced a progressive improvement of symptoms and eGFR, with normalization of tubular dysfunction indices within 6 months. Case 1 did not receive any medication and her renal function normalized after 8 weeks from the acute onset. However, after 7 years from the ATIN diagnosis, the patient was readmitted because of Stage 2 hypertension. She is

Table 1. Clinical and laboratory data of patients at ATIN diagnosis

	Case 1	Case 2	Case 3	Case 4	Case 5
Aetiology	–	–	–	TINU syndrome	Adenovirus infection
Renal units	2	2	2	2	1
Age (years)	3	16	14	12	17
Body weight (kg)	15.2	58.5	45.2	66	51.1
Gender	Female	Male	Male	Male	Male
eGFR (mL/min/1.73 m^2)	43	57	70	80	32
AKI stage	2	1	1	1	3
CRP (mg/L)	58	15.9	68.4	2.9	49.7
ESR (mm/h)	90	63	25	23	38
Glycosuria	+	+	+	+	+
Proteinuria/U-Cr (mg/mg)	0.21	0.73	0.26	0.25	2.5
U-NAG/U-Cr (U/mmol)	5.1	3.7	2.7	2.5	2
U-A1M (mg/day)	125.2	86.8	55.8	34.4	216.6
FENa (%)	1	1.9	0.9	1	1.9
FEK (%)	31	52	12	13	18

U-Cr, urinary creatinine; U-NAG, urinary *N*-acetyl-β-D-glucosaminidase (normal value <0.5 U/mmol of urinary creatinine); U-A1M, urinary alpha 1 microglobulin (normal value = 0–17 mg/day); FENa, fractional excretion of sodium; FEK, fractional excretion of potassium.

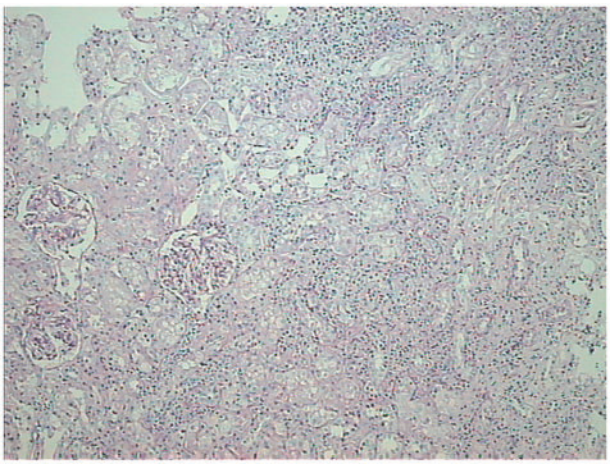

Fig. 1. Patchy inflammatory infiltrate between the cortical tubules, without glomerular lesions. Image refers to renal biopsy performed in Case 1. Periodic acidSchiff stain ×10.

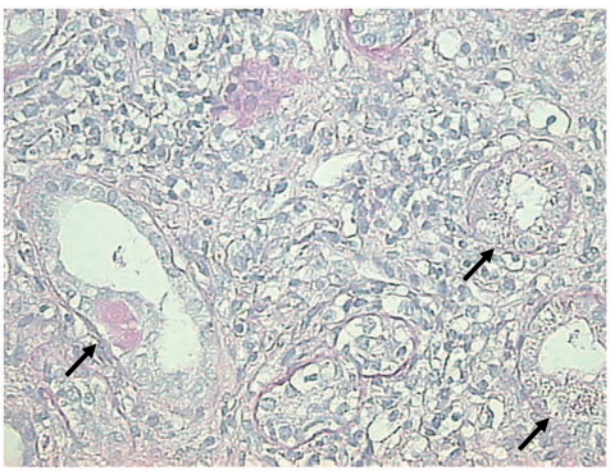

Fig. 2. Acute tubular lesions, with loss of brush-border and presence of granular inclusions (arrows) suggesting epithelial regeneration. Image refers to renal biopsy performed in Case 3. Periodic acidSchiff stain ×40.

currently receiving amlodipine plus ramipril and her blood pressure is within the normal range. Due to the persistence of mild symptoms and AKI, after renal biopsy findings evaluation, Cases 2 and 3 were both treated with oral prednisone at an initial dose of 60 mg/m^2, tapered over 8 weeks, with subsequent rapid recovery. Their eGFR is currently normal after 36 and 18 months of follow-up, respectively. Case 4 did not receive oral steroids, but did receive prednisolone acetate drops because of acute anterior uveitis. Topical corticosteroid tapering was associated with a flare; therefore, difluprednate was started and maintained for 2 weeks. After >18 months of follow-up, this patient did not experience other acute uveitis relapses. All medications were tapered and no residual inflammation was present at the last ophthalmological exam. The transplanted patient (Case 5) was diagnosed with an adenovirus-related ATIN. Therefore, the chronic immunosuppressive regimen was simplified by suspending mycophenolate mofetil, while continuing tacrolimus and prednisone (10 mg/day). Moreover, the patient was treated with oral ribavirine (200 mg every 6 h) for 1 month. This resulted in normalization of inflammatory and tubular markers, negativization of adenovirus RT-PCR assay, but incomplete recovery of renal function. Shortly after ATIN, the patient experienced an acute humoral rejection that was treated with plasma exchange, intravenous immunoglobulins and rituximab. A renal biopsy performed after 2 years after the ATIN diagnosis showed findings of chronic allograft nephropathy. The eGFR is currently 30 mL/min/1.73 m^2 at 5 years after kidney transplantation and 3 years after ATIN.

DMSA renal scans

DMSA renal scans performed during the acute phase of ATIN revealed suggestive findings, including diffuse reduction of the renal radionuclide uptake and presence of multiple 'cold' focal lesions spread within the parenchyma in a patchy and corticomedullary distribution (Table 2; Figures 3a and 4a; Supplementary data, Figures S1a, S2a and S3a). The extension and number of renal hypoactive areas seemed to correlate with the degree of renal dysfunction. Renal radionuclide uptake was almost normal in Cases 3 and 4, who showed only mild impairment in renal function (Figure 4a; Supplementary data, Figure S2a).

Table 2. Renal DMSA scan findings in acute phase of ATIN and at follow-up

Findings	Case 1	Case 2	Case 3	Case 4	Case 5
Acute scan					
Diffuse hypo uptake of radionuclide	+	+	−	−	+ (1 renal unit)
Number of focal lesions	>10	>10	8	1	2
Control scan					
Time from ATIN diagnosis (months)	92	12	12	12	16
Number of scars	4	0	0	0	2

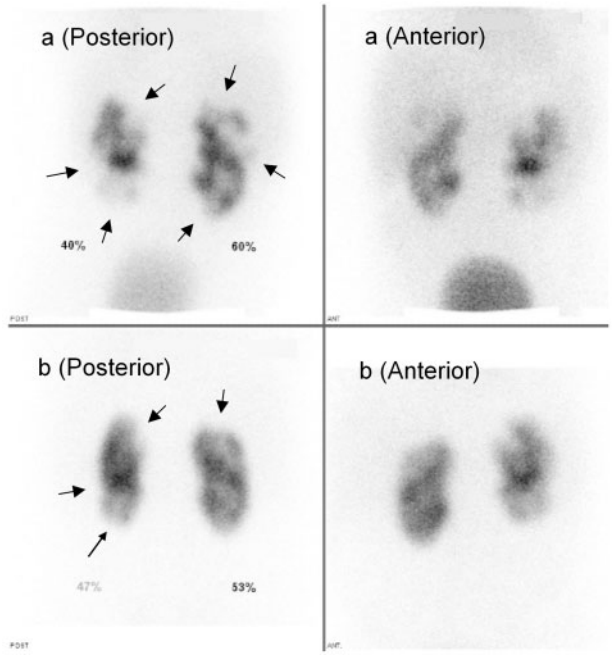

Fig. 3. (**a**) Acute and (**b**) control renal DMSA scans performed in Case 1. The acute scan shows several 'cold' focal lesions in both kidneys and a diffuse reduction of the renal uptake of radionuclide. The lesions involve both cortex (arrows) and medulla. The control scan performed after >7 years from ATIN shows persistence of four cortical defects (arrows).

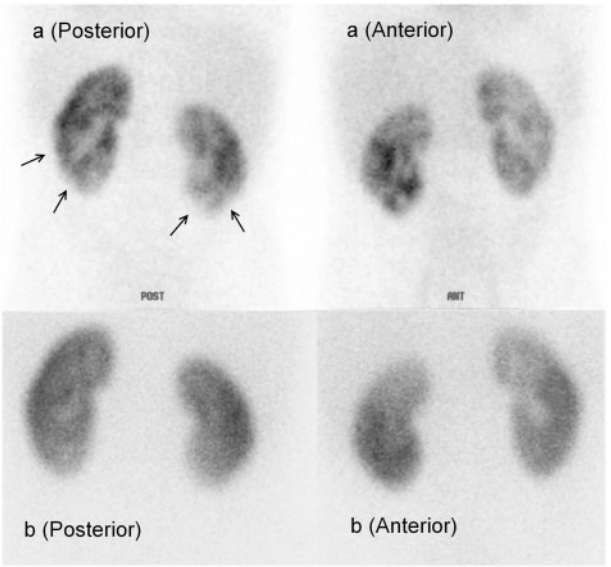

Fig. 4. (**a**) Acute and (**b**) control renal DMSA scans performed in Case 3. The acute scan shows 'cold' focal lesions localized bilaterally and involving both cortex (arrows) and medulla with a patchy distribution. The control scan shows a normalized pattern of radionuclide uptake.

All patients had repeated a control DMSA scan after a median time of 12 months (range 12–92) from the ATIN diagnosis. DMSA renal scans resulted normal in three patients (Figure 4b; Supplementary data, Figures S1b and S2b), whereas uptake defects persisted in two patients (Cases 1 and 5). In Case 1, the scintigraphy was performed 7 years after the acute phase, when the patient was hypertensive, and it showed an improvement in the overall renal uptake of radionuclide, but persistence of several cortical defects (Figure 3b). In the transplanted patient, the control scan was performed 12 months after ATIN and also showed renal scarring (Supplementary data, Figure S3b).

Discussion

In this study, we described clinical characteristics and outcome of five children diagnosed with ATIN. We were able to identify a peculiar DMSA renal scan pattern in the acute phase of ATIN and we also demonstrated the usefulness of DMSA scintigraphy in the follow-up evaluation.

Diagnosis of ATIN is often a challenge because this syndrome is characterized by a wide spectrum of signs, symptoms and laboratory findings [4]. The nonspecific nature of clinical findings and laboratory tests entails a central diagnostic role of renal biopsy, especially in uncertain and severe cases with prolonged renal dysfunction. Various studies have evaluated the role of US in the diagnosis of AKI. US allows a simple and noninvasive evaluation of kidneys; however, in case of acute renal dysfunction, US findings are highly nonspecific and kidneys may appear either normal or moderately increased in size, with an increase in their echogenicity due to the presence of inflammatory infiltrate [17].

Few reports have suggested that Ga-67 scintigraphy may be a valuable tool in both diagnosis and follow-up of ATIN [8–12]. Ga-67 acts as an iron analogue and has high affinity for lactoferrin. In ATIN, leucocytes in the interstitial space may degranulate and release a large quantity of iron-binding lactoferrin with subsequent localization of Ga-67 in kidney tissue. In both experimental models and patients with unexplained AKI, Ga-67 scan has been used to differentiate between ATIN and acute tubular necrosis. In 44 patients with various biopsy-proven forms of acute renal dysfunction, Linton *et al.* found an intense, diffuse and bilateral renal Ga-67 uptake in all cases with drug-induced ATIN, whereas no significant renal gallium uptake was found in patients with acute tubular necrosis [9]. Contrasting results were obtained by two other small studies that reported a low sensitivity of Ga-67 scintigraphy in the diagnosis of ATIN [18, 19]. Very recently, Graham *et al.* described 76 patients who underwent Ga-67 scintigraphy for suspicion of ATIN [12]. Intensity of radioisotope uptake in the kidney was graded from 0 to 5 and, when using a cut-off value of 3, the authors obtained

a sensitivity of 61% and a specificity of 75% for the diagnosis of ATIN. In addition to a controversial diagnostic performance, the use of Ga-67 citrate in children is questionable because of its radiation effective dose, which is at least 10 times higher than that of ^{99m}Tc DMSA (30 mSv versus 1–3 mSv), due to higher energy and longer half-life (78 h versus 6 h) [14, 20].

To our knowledge, no studies have previously assessed the diagnostic significance of DMSA scan in the diagnosis and follow-up of ATIN. DMSA scintigraphy is indicated in children for evaluation and/or detection of acute pyelonephritis, renal scars, small kidneys, duplicated collecting systems, renal masses and systemic hypertension [15]. ^{99m}Tc DMSA is a renal cortical scanning agent that localizes in the proximal tubules. The tubular cells of the *pars recta* take up the tracer directly from the peritubular vessels. To investigate the mechanisms of tubular uptake, in 1985, Provoost and Van Aken induced a generalized proximal tubular dysfunction in rats by administering sodium maleate and found a 31.5% decrease in the amount of ^{99m}Tc DMSA retained in the kidney with a 23.3% increase in the amount found in the bladder [21]. They speculated that this enhanced excretion was caused by either an inhibition of tubular reabsorption or a rapid cellular release. Poor renal uptake of ^{99m}Tc DMSA had been reported in one patient with a diagnosis of cystinosis [22] and in four cases of juvenile nephronophthisis [23], both hereditary conditions that are associated with chronic tubulointerstitial changes. According to these authors, ^{99m}Tc DMSA uptake is an index of functioning tubular mass rather than global renal function and therefore correlates with the predominant tubulointerstitial disease. In our series of one patient with a clear clinical diagnosis and four patients with a biopsy-proven diagnosis of ATIN, we found a suggestive DMSA scan pattern characterized by multiple focal areas of reduced radionuclide uptake spread into the renal parenchyma. This is consistent with the patchy distribution of acute tubulointerstitial inflammation, as was demonstrated by histological findings. In patients with a moderate to severe impairment of renal function, 'cold' lesions were larger and also associated with a diffuse reduction in the uptake of radionuclide.

Clinically, subacute symptoms, persistence of the potentially offending agent (i.e. medications) and a prolonged renal dysfunction are related to a more chronic course of ATIN [24]. In histology, tubular atrophy, interstitial granuloma and pronounced interstitial cell infiltration indicate chronicity. These findings are comparable to those observed in renal scarring after acute pyelonephritis, where it is widely accepted that DMSA scan represents the most sensitive method for non-invasive detection [25]. In our series, a control DMSA scan performed after a median time of 12 months from the diagnosis of ATIN allowed the identification of renal scars in two patients, Cases 1 and 5, who showed a more severe functional impairment during the acute phase. In Cases 2 and 3, both treated with steroids, a complete normalization of scintigraphic pattern was found, as it also was in Case 4, who only exhibited a mild decrease of eGFR in the acute phase.

Our study suggests that DMSA scan, in addition to renal biopsy, may be a useful tool in the diagnostic process of ATIN in children. Moreover, the comparison of DMSA scan images in the acute phase with those obtained from a follow-up scintigraphy allows monitoring of the evolution of renal parenchymal inflammation with potential risk of chronic damage due to renal scarring. The most important limitation of our study is the small sample size, but we believe that our cumulative observations may be useful in clinical practice and we hope they will generate further research in this area. Our pilot findings warrant further assessment in a larger study for validation.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

Conflict of interest statement

None declared.

References

1. Greising J, Trachtman H, Gauthier B *et al*. Acute interstitial nephritis in adolescents and young adults. *Child Nephrol Urol* 1990; 10: 189–195
2. Lanewala A, Mubarak M, Akhter F *et al*. Pattern of pediatric renal disease observed in native renal biopsies in Pakistan. *J Nephrol* 2009; 22: 739–746
3. Li Z, Kang Z, Duan C *et al*. Clinical and pathological features of acute kidney injury in children. *Ren Fail* 2014; 36: 1023–1028
4. Ulinski T, Sellier-Leclerc AL, Tudorache E *et al*. Acute tubulointerstitial nephritis. *Pediatr Nephrol* 2012; 27: 1051–1057
5. Corwin HL, Korbet SM, Schwartz MM. Clinical correlates of eosinophiluria. *Arch Intern Med* 1985; 145: 1097–1099
6. Praga M, González E. Acute interstitial nephritis. *Kidney Int* 2010; 77: 956–961
7. Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. *Clin J Am Soc Nephrol* 2013; 8: 1857–1862
8. Wood BC, Sharma JN, Germann DR *et al*. Gallium citrate Ga 67 imaging in noninfectious interstitial nephritis. *Arch Intern Med* 1978; 138: 1665–1666
9. Linton AL, Richmond JM, Clark WF *et al*. Gallium67 scintigraphy in the diagnosis of acute renal disease. *Clin Nephrol* 1985; 24: 84–87
10. Shibasaki T, Ishimoto F, Sakai O *et al*. Clinical characterization of drug-induced allergic nephritis. *Am J Nephrol* 1991; 11: 174–180
11. Joaquim AI, Mendes GE, Ribeiro PF *et al*. Ga-67 scintigraphy in the differential diagnosis between acute interstitial nephritis and acute tubular necrosis: an experimental study. *Nephrol Dial Transplant* 2010; 25: 3277–3282
12. Graham F, Lord M, Froment D *et al*. The use of gallium-67 scintigraphy in the diagnosis of acute interstitial nephritis. *Clin Kidney J* 2016; 9: 76–81
13. Lassmann M, Biassoni L, Monsieurs M *et al*.; EANM Dosimetry and Paediatrics Committees. The new EANM paediatric dosage card. *Eur J Nucl Med Mol Imaging* 2007 34: 796–798
14. Chu KH, Lin YT, Hsu CC *et al*. Evaluation of effective dose for a patient under Ga-67 nuclear examination using TLD, water phantom and a simplified model. *J Radiat Res* 2012; 53: 989–998

15. Piepsz A, Colarinha P, Gordon I *et al.*; Paediatric Committee of the European Association of Nuclear Medicine. Guidelines for 99mTc-DMSA scintigraphy in children. *Eur J Nucl Med* 2001; 28: BP37–BP41
16. Schwartz GJ, Muñoz A, Schneider MF *et al*. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; 20: 629–637
17. Hiraoka M, Hori C, Tsuchida S *et al*. Ultrasonographic findings of acute tubulointerstitial nephritis. *Am J Nephrol* 1996; 16: 154–158
18. Graham GD, Lundy MM, Moreno AJ. Failure of gallium-67 scintigraphy to identify reliably non-infectious interstitial nephritis: concise communication. *J Nucl Med* 1983; 24: 568–570
19. Koselj M, Kveder R, Bren AF *et al*. Acute renal failure in patients with drug-induced acute interstitial nephritis. *Ren Fail* 1993; 15: 69–72
20. Smith T, Evans K, Lythgoe MF *et al*. Radiation dosimetry of technetium-99m-DMSA in children. *J Nucl Med* 1996; 37: 1336–1342
21. Provoost AP, Van Aken M. Renal handling of technetium-99m DMSA in rats with proximal tubular dysfunction. *J Nucl Med* 1985; 26: 1063–1067
22. De Geeter F, Saelens E, Van Steelanch H *et al*. Differential renal uptake of technetium-99m-DMSA and technetium-99m-DTPA. *J Nucl Med* 1993; 34: 1217–1218
23. Hecht H, Ohlsson J, Starck SA. Poor renal uptake of ^{99m}technetium-dimercaptosuccinic acid and near-normal ^{99m}technetium-mercaptoacetyltriglycine renogram in nephronophthisis. *Pediatr Nephrol* 1996; 10: 167–170
24. Schwarz A, Krause PH, Kunzendorf U *et al*. The outcome of acute interstitial nephritis: risk factors for the transition from acute to chronic interstitial nephritis. *Clin Nephrol* 2000; 54: 179–190
25. Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. *J Urol* 2010; 184: 265–273

Clinical Kidney Journal
ckj