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Ga-67 scintigraphy in the differential diagnosis between acute interstitial nephritis and acute tubular necrosis: an experimental study

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Abstract

Background. The differentiation between acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) is crucial in patients with acute kidney injury. Gallium-67 citrate (Ga-67) has been used clinically in the differential diagnosis between these entities, but its efficacy is disputed. The aim of this study was to evaluate Ga-67 scintigraphy efficacy in the differentiation between experimental models of drug-induced AIN and ATN.

Methods. Animals were divided into three groups: AIN (n = 8), ATN (n = 8) and control (NL, n = 10). The AIN group received intraperitoneal puromycin aminonucleoside (single dose, 150 mg/kg). The ATN group received a single intraperitoneal injection of cisplatin (6 mg/kg). The NL group did not receive active drugs. All of the animals were submitted to Ga-67 scintigraphy, serum creatinine (Cr) and urinary osmolality assessment, and blinded renal histology evaluation.

Results. Renal Ga-67 uptake was strikingly more intense in the AIN group when compared to the ATN ($P < 0.0001$) and NL ($P < 0.001$) groups. The ATN group had increased Cr when compared to the NL group ($P < 0.001$) and lower urinary osmolality *vs* the NL ($P < 0.001$) and AIN ($P < 0.01$) groups. Renal histology showed severe acute tubular injury in the ATN group and intense interstitial inflammation in the AIN group, and was normal in control animals.

Conclusion. Ga-67 scintigraphy was extremely effective in the differentiation between experimental drug-induced ATN and AIN.

Keywords: acute interstitial nephritis; acute kidney injury; acute tubular necrosis; experimental study; Ga-67 scintigraphy

Introduction

The correct differentiation between acute tubular necrosis (ATN), the major cause of acute kidney injury (AKI) in hospitalized patients [1], and drug-induced acute interstitial nephritis (AIN) is extremely important. AIN represents ~3% of all renal biopsies [2,3]. Drug-induced AIN is the

most usual form of AIN and corresponds to 5–15% of AKI cases [3,4]. The clinical picture and laboratory pattern of AIN and ATN are usually very similar. The urinary abnormalities supposedly related to AIN such as sterile pyuria, mild proteinuria and eosinophiluria lack sensitivity and specificity [2–5]. In drug-induced AIN, allergic manifestations such as fever, arthralgia and skin exanthema were observed in only 5–10% of the cases [4,6]. The early diagnosis of drug-induced AIN is particularly important, since the causal agent must be removed, and timely steroid therapy may influence renal function recovery [7,8]. Renal biopsy is currently considered as the gold standard for the precise diagnosis of AIN. The lesion is characterized by intense renal interstitial infiltrate, especially of mononuclear cells and T lymphocytes, with a variable number of plasmocytes and eosinophils [2–4]. However, renal biopsy is an invasive procedure, with potential side effects such as pain, haematuria, bleeding and even nephrectomy, and is usually difficult to perform in severely ill patients in the intensive care unit. Ga-67 scan has been pointed as a possible non-invasive, safer and less expensive alternative to discriminate between AIN and ATN [4,6,9].

The objective of this study was to assess the efficacy of Ga-67 scintigraphy in the discrimination between drug-induced ATN and AIN using experimental rodent models.

Materials and methods

Rats

Twenty-six Munich–Wister male rats, with baseline weight ranging from 200 to 300 g, from the animal facility, São José do Rio Preto Medical School (FAMERP) were used. The study was approved by the Animal Experimentation Ethics Committee (CEEA), FAMERP. During the experiment, the animals were maintained in boxes containing two to three animals, and received normal salt and protein diet (Labina–Purina®, Brazil) and tap water *ad libitum.* All of the animals were treated according to the recommendations of the Committee on Care and Use of Laboratory Animals—Institute of Laboratory Animal Resources (ILAR), USA [10].

Experimental groups

Animals were divided into three groups: AIN, ATN and control (NL).

AIN

Eight animals received a single, intraperitoneal injection of puromycin aminonucleoside (Sigma-Aldrich Chemical Company, St. Louis, MO, USA), at the dose of 15 mg/100 g of body weight diluted in saline solution (NaCl 0.9 g/100 mL) [11]. Animals were evaluated 14 days after puromycin injection. This interval was chosen because it is the time point of maximal inflammatory interstitial injury [11].

ATN

ATN induction was performed in eight animals using a single intraperitoneal injection of cisplatin (Eurofarma Laboratórios Ltda, São Paulo, SP, Brazil), at the dose of 6 mg/kg of body weight diluted in saline solution (NaCl 0.9 g/100 mL). Animals were studied 8 days after cisplatin injection at the time point of maximal tubular injury.

Control group

The 10 animals in this group were not submitted to any therapy.

Study design

All animals received a single intraperitoneal dose of 11.1 MBq (300 μCi) of Ga-67 (Centro de Radiofarmacia, IPEN, Sao Paulo, SP, Brazil) 14 days after the injection of puromycin aminonucleoside (AIN group) and 8 days after cisplatin injection (ATN group). In the control group, the experiment started with the administration of this drug.

After the injection of Ga-67, animals were placed in metabolic cages (Nalgene, Nalge Company, Rochester, NY, USA) for 24 h, and urinary volume was collected during this period. The urine sample was centrifuged and used for biochemical dosages.

Scintigraphy was performed with a digital gamma camera SPX4-Elscint (Haifa, Israel), provided with a medium, circular field detector, attached to a high-resolution collimator. A 10% energy window centred over 93, 184 and 300 keV (^{67}Ga photopeaks), with a matrix of 128 × 128 and magnification of three times, was used. To obtain images, animals were anaesthetized with an intraperitoneal injection of a 50-mg/mL/kg solution of sodium thiopental. Static images were obtained 48 h after the administration of the radiopharmaceutical with animals in decubitus dorsalis for 10 min.

After images were obtained and while the animals were still anaesthetized, a catheterization (PE50) of the right carotid artery was performed to obtain blood samples for biochemical measurements.

At the end of the experiment, animals were euthanized, and the left kidney was removed and prepared for histology evaluation.

Scintigraphy

Regions of interest (ROI) in the kidney and liver were designed in the images in order to obtain the counts per region. Semi-quantitative analysis was performed dividing the counts per region of the kidney by the counts per region of the liver.

Biochemical dosages

Urine and plasma were used for the following dosages: 24-h proteinuria by the colorimetric method (Dimension RXL, Dade Behring, Newark DE, USA), potassium by electrolyte analyser (9180, Electrolyte Analyzer, AVL Scientific Co., Roswell GA, USA), creatinine by the alkaline picrate method (Jaffé, analysed by spectrophotometer BTS 310 ByoSystems, Barcelona, Spain) and osmolality by freezing point osmometer (Osmette A, Precision Systems, Natick, MA, USA).

Renal histology

The kidney was sectioned longitudinally, fixed in 10% formaldehyde solution and diluted in 10% of saline solution 0.9%. The material was embedded in paraffin, and 3–4-μm sections were obtained, identified, and stained by haematoxylin–eosin (HE), Masson's trichrome (MT) and periodic acid–methenamine silver (PAMS). Histological analysis was performed by a single pathologist (M.A.F.B.) who was blinded for the study groups. The following parameters were analysed semi-quantitatively (+ a 4+): interstitial infiltrate by mononuclear and/or polymorphonuclear cells, tubular dilation, epithelial thinning, tubular necrosis in cortical, juxtamedullary and medullar areas, or diffuse tubular necrosis, and acute epithelial degenerative changes [12].

Statistical analysis

Results are presented as mean ± SE. Variance analysis (ANOVA) was used for group analyses followed by a Student–Newman–Keuls *post hoc* test or Kruskal–Wallis' test followed by Dunn's multiple comparison *post hoc* test, as appropriate. $P < 0.05$ was considered statistically significant.

Results

Ga-67 uptake

The visual analysis showed clearly that renal uptake of Ga-67 was remarkably more intense in the AIN group when compared to the ATN and control groups (Figure 1).

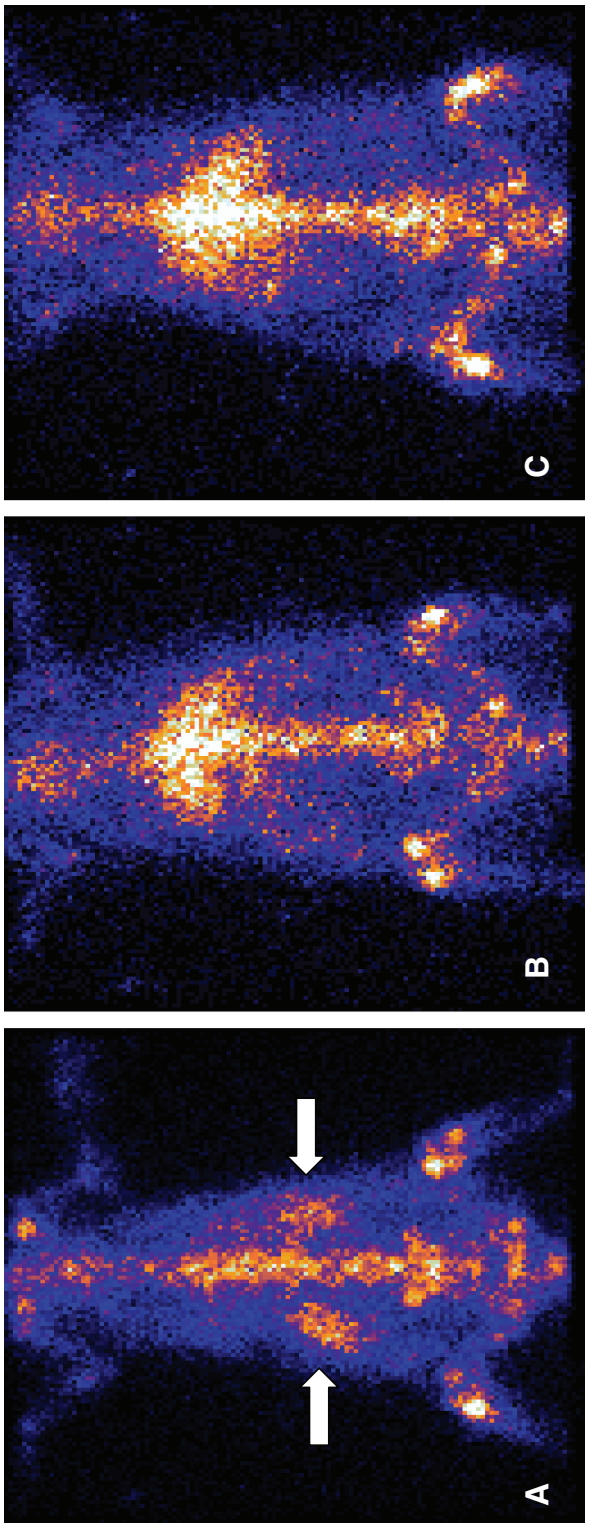

Fig. 1. Renal Ga-67 scintigraphy in rats in the AIN group (**A**) showing a striking uptake of the marker (white arrows) in frank contrast with the ATN (**B**) and NL (**C**) groups with no uptake (left kidney).

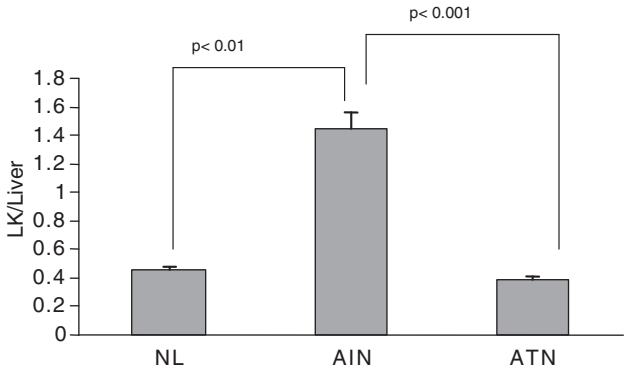

Fig. 2. Quantification of Ga-67 uptake in NL, AIN and ATN group rats (left kidney).

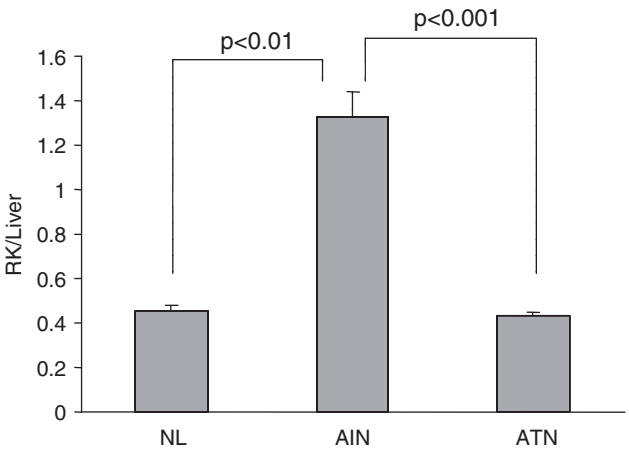

Fig. 3. Quantification of Ga-67 uptake in NL, AIN and ATN group rats (right kidney).

The semi-quantitative analysis confirmed these results. Mean left kidney uptake was 0.46 ± 0.02 in the control group, 1.45 ± 0.12 in the AIN group and 0.39 ± 0.02 in the ATN group. Mean right kidney uptake was 0.46 ± 0.02 in the control group, 1.33 ± 0.11 in the AIN group and 0.43 ± 0.02 in the ATN group. The comparison of mean values of renal uptake of Ga-67 in the three groups showed a significant difference between the NL and AIN groups ($P < 0.01$ for both kidneys) and between AIN and ATN ($P < 0.001$ for both kidneys). There was no difference between the renal uptake in both kidneys when the NL and ATN groups were compared (Figures 2 and 3).

Renal function assessment

Renal function results of the three study groups are shown in Table 1. Urinary volume was similar in NL and AIN groups, and significantly higher ($P < 0.001$ *vs* NL) in the ATN group. Proteinuria was small and similar in the NL and ATN groups, and significantly elevated in the AIN group ($P < 0.01$ *vs* NL). Plasma potassium was significantly elevated in the ATN group as compared to NL and AIN groups and 4.7 ± 0.3 mEq/L in the ATN group. Plasma creatinine was significantly increased in the ATN group as compared to NL animals. Urinary osmolality was significantly lower in the ATN and AIN as compared to the NL group. Additionally, urinary osmolality was significantly lower in the ATN group when compared to the AIN group.

Histological analysis

Table 2 shows the histological findings of the experimental groups. In the AIN group ($n = 8$), significant interstitial infiltrates was observed in 100%, tubular dilation in 75% of the animals and moderate epithelial thinning in 37.5% of them (Figure 4). There was no necrosis or acute epithelial degenerative changes in this group, and hyaline deposition in the tubular lumen was observed in only one rat. On the other hand, in the ATN group ($n = 8$), histological findings included severe tubular epithelial thinning and dilation in 87.5% of the animals, moderate tubular necrosis and acute epithelial degenerative changes in 50% of the rats, and mild interstitial infiltrate in 37.5% of the them (Figure 4). The interstitial infiltrate was significantly higher in the AIN group when compared to NL and ATN groups. Conversely, tubular injury was significantly more intense in the ATN group. The control group ($n = 10$) had normal renal histology, without any significant change (Figure 4).

Discussion

This study showed that renal Ga-67 scintigraphy was extremely effective to differentiate AIN injury from ATN and normal kidneys. Whereas there was a uniformly high positive Ga-67 uptake in the kidneys of animals with AIN, renal scintigraphy was negative in the ATN and control

Table 1. Urinary volume, 24-h proteinuria, plasma potassium, plasma creatinine and urinary osmolality in the control, AIN and ATN groups

	Experimental group		
	NL	AIN	ATN
Urinary volume (mL)	11.5 ± 0.9*	19.6 ± 2.4	32.9 ± 2.8
24-h proteinuria (mg/24 h)	9.6 ± 2.3**	610 ± 56	14.2 ± 1.7
Plasma K (mEq/L)	3.4 ± 0.1***	3.8 ± 0.2	4.7 ± 0.3****
Plasma Cr (mg/dL)	0.55 ± 0.05*	0.78 ± 0.11	0.99 ± 0.07
Urinary Osm (mOsm/kg)	1386 ± 65*,*****	788 ± 56******	513 ± 30

Values are mean ± SE.K, potassium; Cr, creatinine; Osm, osmolality; NL, control group; AIN, acute interstitial nephritis group; ATN, acute tubular necrosis group.*$P < 0.001$ *vs* ATN, **$P < 0.01$ *vs* AIN, ***$P < 0.01$ *vs* ATN, ****$P < 0.05$ *vs* AIN, *****$P < 0.001$ *vs* AIN, ******$P < 0.01$ *vs* ATN.

Table 2. Renal histology scores in the AIN, ATN and control groups

	Experimental group		
	NL	AIN	ATN
Interstitial infiltrate	0	1.75 ± 0.25*,**	0.38 ± 0.18
Epithelial thinning	0	0.63 ± 0.32*	2.5 ± 0.46
Tubular dilation	0	0.88 ± 0.23	2.25 ± 0.45
Tubular necrosis	0	0	1.25 ± 0.37
Acute epithelial degenerative changes	0	0	1.25 ± 0.49

Values are mean ± SE.NL, control group; AIN, acute interstitial nephritis group; ATN, acute tubular necrosis group; 0, no changes in this group. *P < 0.05 *vs* ATN, **P < 0.001 *vs* NL.

groups. To the best of our knowledge, there are no other studies on the efficacy of Ga-67 renal uptake for differentiation between experimental models of AIN and ATN.

The use of experimental models of AIN and ATN allowed to test Ga-67 scintigraphy in the time points when the renal lesion to be studied was more intense, in flagrant difference to the clinical situation. In fact, it is very unusual to perform renal biopsies in the early phases of AKI.

Ga-29 is an analogue to ions of iron, and when administered IV, 90% of the injected dose circulates in the plasma bound to plasma proteins, especially transferrin [13]. Ionic status or transferrin-bound Ga-67 probably reaches the site of inflammation and the extracellular fluid through loose endothelial connections. When an inflammatory lesion is present, this space is rich in lactoferrin (produced by leucocytes) and siderophores (produced by bacteria and fungi), both iron-binding compounds, favouring the uptake of Ga-67 [14]. The presence of inflammatory cells into the interstitial area is also related to Ga-67 accumulation. Lymphocytes B have lactoferrin-binding sites on their surface with high Ga-67 affinity, and macrophages loaded with protein, iron complexes and cellular waste accumulate Ga-67 [13,15].

The puromycin aminonucleoside (PAN) was selected as a model of AIN because it produces an intense renal interstitial mononuclear cell infiltrate, reaching maximal intensity on experiment Day 14 [16]. This infiltrate is characterized by T lymphocytes, especially cytotoxic T cells, and by a large macrophage influx [17]. Indeed, in the present study, a severe AIN with intense inflammatory cells infiltrate was observed 14 days after PAN injection. Cisplatin was selected as an ATN model because it causes ATN in a consistent way, with maximal tubular injury and mild interstitial inflammation occurring at ~8 days after its administration. Cisplatin-induced AKI is non-oliguric with mild proteinuria, as observed in the ATN group. Renal histology confirmed the efficacy of the utilized models. Animals treated with puromycin aminonucleoside developed intense AIN, and those treated with cisplatin developed severe ATN.

Case reports and clinical studies have reported the successful use of Ga-67 in the differential diagnosis of ATN and AIN in AKI patients [9,18–25]. Wood *et al.* [19] were the first to describe a positive renal uptake of Ga-67 in three cases of non-infectious interstitial nephritis. Linton *et al*. [20] investigated patients with renal diseases undergoing Ga-67 scan and observed intensive renal uptake of this radiopharmaceutical in individuals with AIN and no uptake in individuals with ATN. In a second study, the same

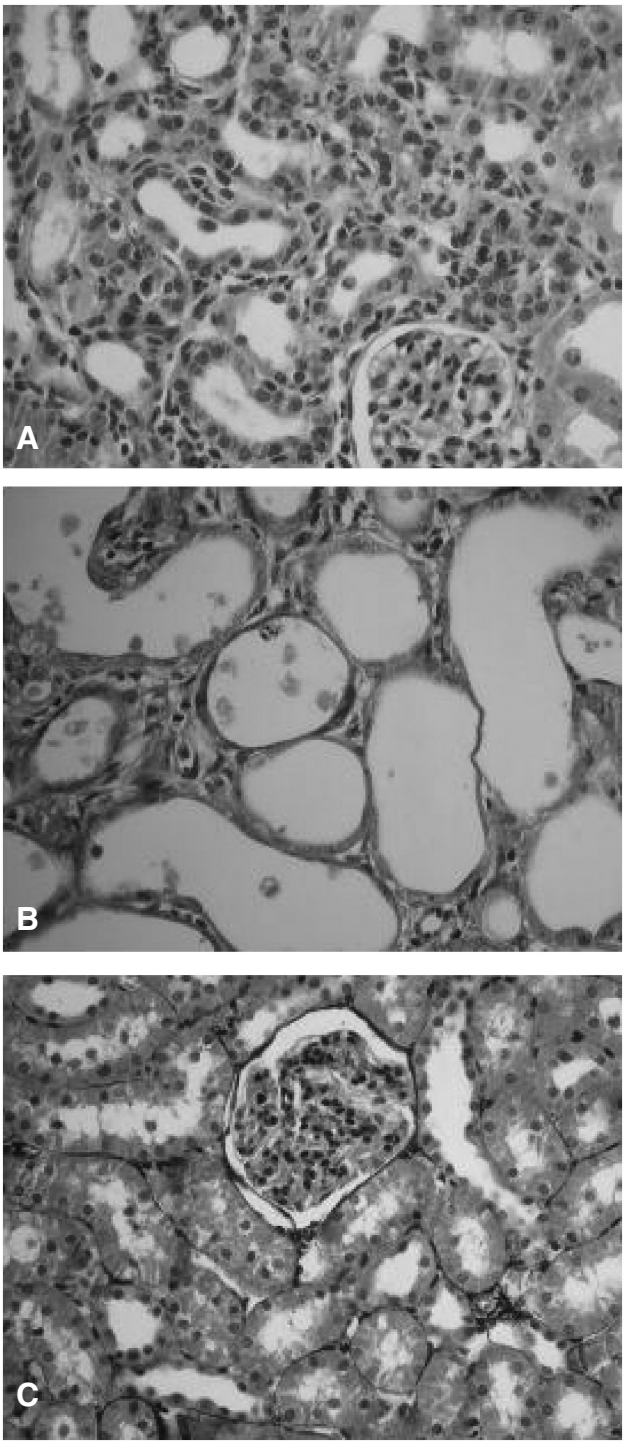

Fig. 4. (**A**) AIN group: renal histology showing intense mononuclear interstitial infiltrate (PAMS ×200); (**B**) ATN group: renal histology showing acute tubular injury, tubular dilation and thin epithelium (PAMS ×400). (**C**) Control rats with normal renal histology (HE ×200).

authors evaluated renal biopsies from AKI patients with intense renal uptake of Ga-67, founding a sensitivity of 100% and specificity of 84% for the diagnosis of AIN by Ga-67 scan [21]. The false positive cases had glomerulonephritis, pyelonephritis, chronic interstitial nephritis, or even no renal disease. Investigating 500 Ga-67 scans in 996 kidneys, Lin *et al*. [22] identified 56 patients with some degree of

renal uptake of this tracer. The authors showed that no uptake or minimal uptake was observed in 94.4% of the kidneys and that 5.6% of the kidneys had increased uptake 48 h after Ga-67 administration. In this group, 10 patients had AIN. There was a mild and unilateral Ga-67 uptake in only one case of ATN.

Failure of the use of Ga-67 in the differential diagnosis of ATN and AIN was also reported. Graham *et al*. studied 12 patients with non-infectious interstitial nephritis confirmed by renal biopsy [23]. There was no Ga-67 uptake in five of these patients and intensive uptake of the tracer in seven. However, all of the patients had chronic renal failure, which changes the histological architecture of the kidney and may interfere with the pattern of interstitial inflammation. Land *et al.* found a positive Ga-67 scintigraphy in 67% of six patients with biopsy-proven AIN [24]. In the same way, Koselj *et al.* reported a positive Ga-67 uptake in 68% of 16 patients with a drug-induced AIN confirmed by biopsy [25].

The discrepancies among the different clinical studies are probably related to the lack of consistence for the time of renal tissue collection. Usually, kidney biopsies are performed lately in the course of AKI that in the case of AIN will correlate with less intense interstitial inflammation.

This study has some limitations. The experimental model studied was not one of hypersensitivity, which is the most usual in the clinical situation. Moreover, the puromycin aminonucleoside model is characterized by an important proteinuria, which is a rare event in clinical AIN, except in some cases of non-steroidal anti-inflammatory drugs-induced AIN [2,3]. We performed the scintigraphy in the peak of the inflammatory cell infiltration, whereas in the clinical field, the scintigraphy is performed in variable time intervals, and the amount of interstitial infiltrate found in renal biopsies is variable in intensity and diffuseness, depending on the duration of exposure and drug implicated.

Conclusion

Ga-67 scintigraphy was extremely effective in the differentiation of drug-induced AIN and ATN. There was a strikingly higher uptake of Ga-67 in the AIN group when compared to the ATN and control groups. These results suggest that the use of Ga-67 scintigraphy in AIN, when intense renal inflammation is present, might be a useful tool for the differential diagnosis between ATN and AIN in patients with AKI.

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Conflict of interest statement. None declared.

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