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Role of Diethylentriamine Penta-Acetic Acid Renograms in Differentiation between Acute Tubular Necrosis and Acute Rejection in Early Post Allograft Renal Transplantation in A Single Tertiary Center

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ABSTRACT

Background: The diagnosis of a failing renal allograft is a complex process. Radionuclide imaging is a great method that gives additional details about the perfusion and function of the transplant without harming the allograft to avoid invasive renal biopsy and its complications.

Objective: The aim of the current study is the differentiation between acute renal graft rejection and acute tubular necrosis in the early post-transplant period using dynamic 99mTc-DTPA scintigraphy.

Patients and methods: A retrospective study was conducted and included 56 cases suffering from acute deteriorated graft function in first year after renal transplantation. We reviewed their dynamic 99mTc-DTPA images findings which performed at time of graft dysfunction and compared with graft biopsy results as a gold standard.

Results: Acute renal rejection was diagnosed in 16 cases; acute tubular necrosis was evident in 28 cases and 12 cases suffering from both elements. By analysis, the mean ages of cases of acute renal graft rejection were 29.3 (SD 9.4) years, cases of acute tubular necrosis were 30.1 (SD 8.1) years, and cases of both elements were 30.7 (SD 5.6) years old. The scintigraphic results showed perfusion and delayed tracer excretion were the most significant predictors (P-value =0.001). The sensitivity and specificity of renal scintigraphy for the detection of acute tubular necrosis (ATN) were 89.3% and 96.4%, respectively; in acute rejection (AR), were 97% and 99%.

Conclusion: A non-invasive procedure with high sensitivity and specificity to distinguish between acute renal rejection and acute tubular necrosis is dynamic renal scintigraphy using 99mTc-DTPA.

Keywords: Renal Transplantation, Acute rejection, Acute tubular necrosis, Diuretic Renography.

INTRODUCTION

Patients with end-stage renal disease (ESRD) have a potential therapy option in kidney transplantation (KTx) [(1)]. A successful kidney transplant can be complicated by a number of diseases, and proper identification and early detection are essential for the best care and preservation of graft function [(2)]. The current gold standard for identifying transplant dysfunction is a renal biopsy. Although beneficial, a biopsy is not advised due to its intrusive nature, high rates of morbidity, and expensive expense [(3)]. There may also be other issues (such as perirenal hemorrhage, an arteriovenous fistula, a pseudoaneurysm, a rupture of the collecting system, etc.) [(2)].

The role of the radiologist as a member of the multidisciplinary transplantation team is evolving as a result of the rise in demand for renal transplantation [(4)]. Acute tubular necrosis (ATN), delayed graft function (DGF), antibody-mediated rejection (ABMR) or T-cell-mediated rejection (TCMR), and harm from nephrotoxic medications are all examples of medical or parenchymal renal graft problems [(3)].

When evaluating allograft perfusion and function, particularly in the early post-operative period, nuclear medicine is crucial. For the care and follow-up of transplanted kidneys, renal scintigraphy using ^{99m}Tc-diethylentriamine penta-acetic acid (DTPA) is a helpful, noninvasive diagnostic method [(5)].

Acute tubular necrosis (ATN) and acute allograft rejection (AR) are the most frequent causes of decreased renal function in the early postoperative period [(6)]. ATN is more frequent in cadaveric transplants and can develop in up to 15% of individuals after renal transplantation. It may initially result in delayed graft function and demand hemodialysis, but because it is anticipated to go away in a few weeks, it has little impact on the patient's or the graft's life [(7)].

The typical scintigraphic signs of ATN include maintained or barely diminished perfusion but delayed uptake and excretion of tubular secretion agents such as Tc-99m DTPA, along with increasing radiotracer buildup in the renal cortex [(8,9)].

Depending on how it manifests (hyperacute, acute, or chronic), renal transplant rejection is often categorized. Each kind is caused by a distinct mechanism. Renography commonly identifies rejection by diminished perfusion, decreased uptake, and delayed excretion [(8)].

Given that perfusion is less compromised in ATN-affected grafts than in AR-affected grafts, scintigraphic perfusion criteria have been proposed to assist in the differential diagnosis of ATN and AR. Additionally, serial investigations suggest that a steady deterioration in function and inadequate perfusion favor AR [(10)].

Thus, the aim of the study is to differentiate between the perfusion and excretion patterns on early

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post-transplant Tc-99m-DTPA renal scintigraphy in cases of acute rejection versus cases of acute tubular necrosis and predict the prognosis of allograft transplantation.

PATIENTS AND METHODS

Our retrospective study was conducted in a single tertiary referral center, Urology and Nephrology Centre in Mansoura, Egypt. A total of 420 cases underwent renal transplantation between January 2017 and December 2021. Renal scintigraphy would be regularly performed as a baseline examination for transplant patients at our medical facility within the first 24 hours following surgery. Only 56 cases suffered from deteriorated graft function with rising serum creatinine or decreased urine output in the first year after renal transplantation. A retrospective collection of data of 56 patients was recorded, they were transferred to the isotope unit of the radiology department, which conducted core biopsies and ^{99m}Tc-DTPA scintigraphy within a maximum of 5 days between the two procedures.

Post processing interpretation and visual analysis of images were achieved for the diagnosis. The dynamic Tc-99m-DTPA renal scintigraphy studies were analyzed by two radiologists (HG) and (DE) with 30 and 14 years of isotope imaging experience, respectively, and agreed by consensus. They were blinded to the pathological results then were compared with pathological finding reports as a gold standard.

Inclusion criteria: Our study includes adult renal transplant patients subjected to Tc-99m-DTPA renal scintigraphy because of acute post renal transplant complications in the first year post-transplantation, well hydrated patients prior to imaging, good image quality, and patients with available confirmed pathological results.

Exclusion criteria: Patients with bad image quality or non-available confirmed pathological results were excluded.

Sample size: Sample size was calculated using the following formula: N= $[(1.96)^2 *$ anticipated Sn (1-anticipated Sn) * (1-anticipated prevalence)$] / d^2$ where; d=0.1. The renal scintigraphy sensitivity for acute rejection (AR) and acute tubular necrosis (ATN) was 98%, 87%, respectively, obtained from previous research by **Juneja and Sharma**, and finally, the calculated sample size was 56 cases with an anticipated prevalence of 10% [(11)].

Technique of Diuretic Renography (DR):

We used Philips Bright View Dual Head Machine. Radionuclide: ^{99m}Tc $t_{1/2}$: 6 hours, Energies: 140 keV, Type: γ generator. We use the glomerular radiopharmaceutical agent ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid). Prior to imaging, the patient should be well hydrated to enhance kidney function, void before injection, and have Intravenous (IV) cannula fixation.

Patients lie in Supine with camera facing front of the patient then bolus intravenous injection on table of tracer was done with dose of 370 MBq (10 mCi) of ^{99m}Tc–DTPA.

Image acquisition:

Image views are anterior and last for a minimal duration of 20 minutes to draw the renogram curve. Computer acquisition setup: matrix: 128x128, Frame rate: frame/3 seconds in the first minute (vascular phase), followed by 1 frame every 20 seconds for the remaining 19 minutes (excretory phase).

Image processing:

The renal transplant ROIs should be drawn on a summed image at 2-3 minutes for calculation of GFR then background ROIs should surround the kidney outline. The patient's weight and height should be provided for the calculation of the GFR.

Post-processing image interpretation:

The aorta or the iliac arteries were used as benchmarks to qualitatively examine the blood flow phase. When the peak kidney activity was equal to or greater than the peak aortic or iliac activity within six seconds of each other, the renal transplant blood flow was regarded as normal. According to the severity of the flow reduction as determined by the visual inspection, mildly, moderately, and significantly decreased flow were all treated the same. Both qualitative and quantitative evaluations of the pictures and renogram curves were used to interpret the functional phase. Renogram Curve composed of three phases: perfusion (Vascular phase) which represent the vascular radio-activity within the renal vessels at first minute, uptake (Ascending limb): 4 minutes after perfusion and represent the accumulation of isotope in the nephron till reaching its maximum at the peak within 2-3 minutes. The peak, which represents the equalization rate of tubular uptake and renal excretion, and the excretory phase (Descending limb) which represent the renal excretion of isotope were calculated. The machine calculates T ½ values which is normally less than 10 minutes.

Ethical approval:

The study was authorized by the Institutional Review Board of the School of Medicine at the University of Mansoura (Proposal code: "R.22.11.1934.R1"). Participants in the research provided written agreement to take part. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

Statistical analysis:

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Number and percentage were used to describe qualitative data. For non-normally distributed data, the median (minimum and maximum) and mean were used to characterize the data. Once the Shapiro-Wilk test has shown that the data are regularly distributed the standard deviation. For non-normally distributed data, the Kruskal Wallis and Mann Whitney U tests were employed to compare two examined groups and more than two studied groups, respectively. More than two independent groups were compared using the One Way ANOVA test, and pair-wise comparisons were found using the Post Hoc Tukey test. Cross-tabulation was used to calculate Kappa agreement for categorical variables, and the results were classified as follows: Kappa 0 indicates no agreement, Kappa between 0.00 and 0.20 indicates slight agreement, Kappa between 0.21 and 0.40 indicates fair agreement, Kappa between 0.41 and 0.60 indicates moderate agreement, Kappa between 0.61 and 0.80 indicates substantial agreement, and Kappa between 0.81 and 1.00 indicates nearly perfect agreement. P value ≤0.05 was considered to be statistically significant.

RESULTS

Our study included 56 patients suffering from deteriorated graft function as evidenced by increasing serum creatinine and decreased urine output in the first year after renal transplantation. Patients' ages ranged from 19 to 54 years, with a mean age of 30.07 (SD 7.97) years; 52 (92.9%) were male and 4 (7.1%) were female. The demographic and clinical data are illustrated in **Table 1**.

Table (1): Patient demographic, clinical and laboratory findings of the studied cases according to pathology.

Variable	Acute Rejection (AR) N=16	Combined acute tubular necrosis & acute Rejection N=12	Acute Tubular necrosis (ATN) N=28	Test of significance
Age/years (Mean ± SD)	29.38 ± 9.49	30.75 ± 5.64	30.18 ± 8.11	P=0.902
Sex Male Female	13 (81.2%) 3 (18.8%)	12(100%) 0 (0%)	27 (96.4%) 1 (3.6%)	P=0.095
Onset of complications (days) Median (Range)	30 (7-90)	7 (2-30)	12 (2-30)	P<0.001*
Serum creatinine (Mean ± SD)	1.89 ± 0.465	1.92 ± 0.47	1.77 ± 0.29	P=0.478

The diuretic renogram parameters were recorded in addition to the visual analysis of reformatted images to reach the most appropriate diagnosis. The diagnosis of acute rejection was established when there were a significant differences in grades of reduction of the renal blood flow and perfusion, including moderately and severely reduced blood flow) (16 cases) (renal blood flow and function have declined significantly, moderately, severely, or both) (**Figure 1**), While the diagnosis of acute tubular necrosis was evident in (28 cases) when there was normal or slightly reduced blood flow, normal or slightly reduced tracer accumulation, with more obvious impairments to the concentration and excretion phases (**Figure 2**).

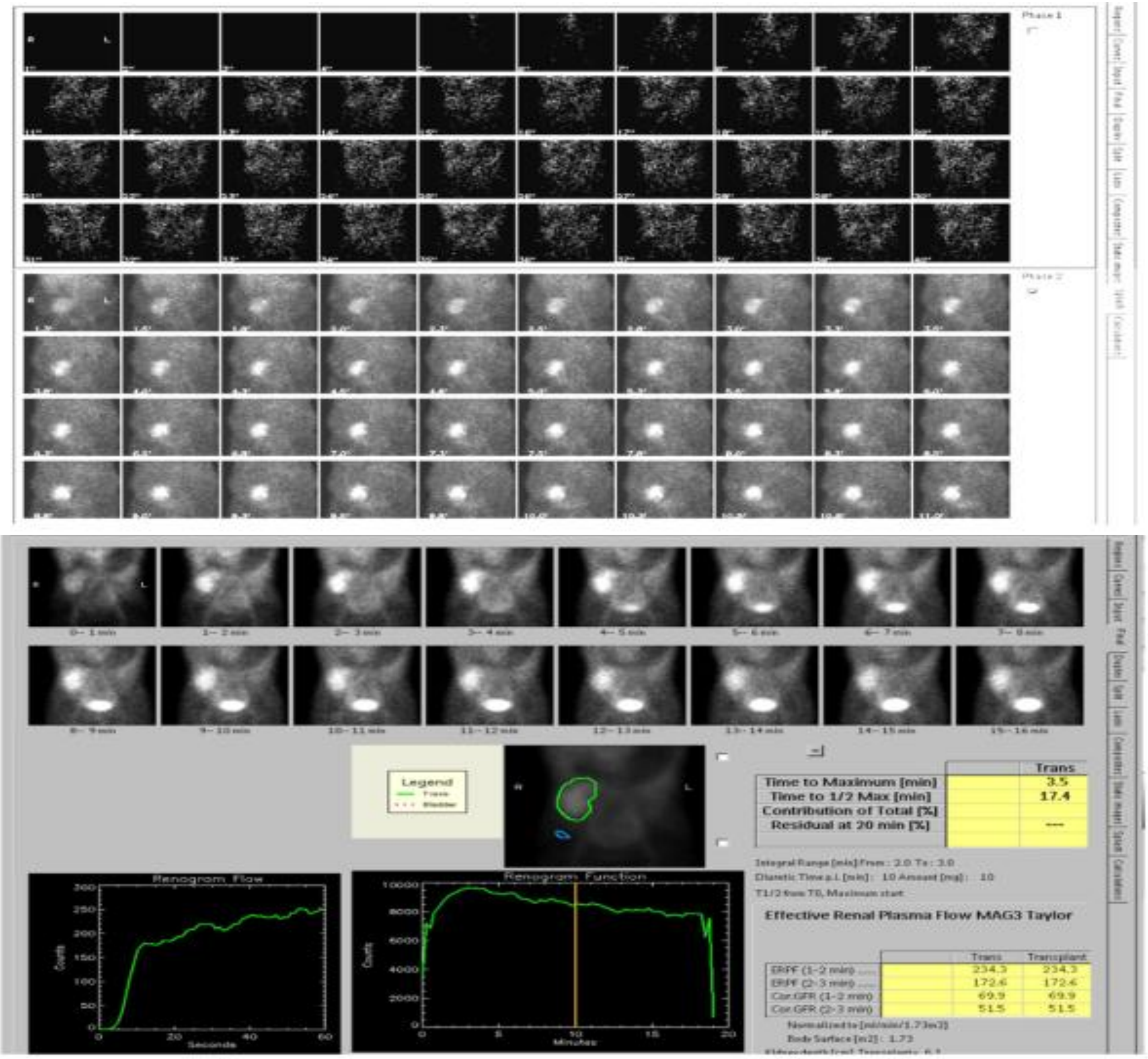

Figure (1): Using ^{99m}Tc-DTPA, a patient with acute rejection had a renal scintigraphic examination. Phase of flow (A). Take note of the flow to the graft's modest diminution. Phase (B) is functional. The radiotracer's concentration, accumulation, and excretion are all somewhat decreased.

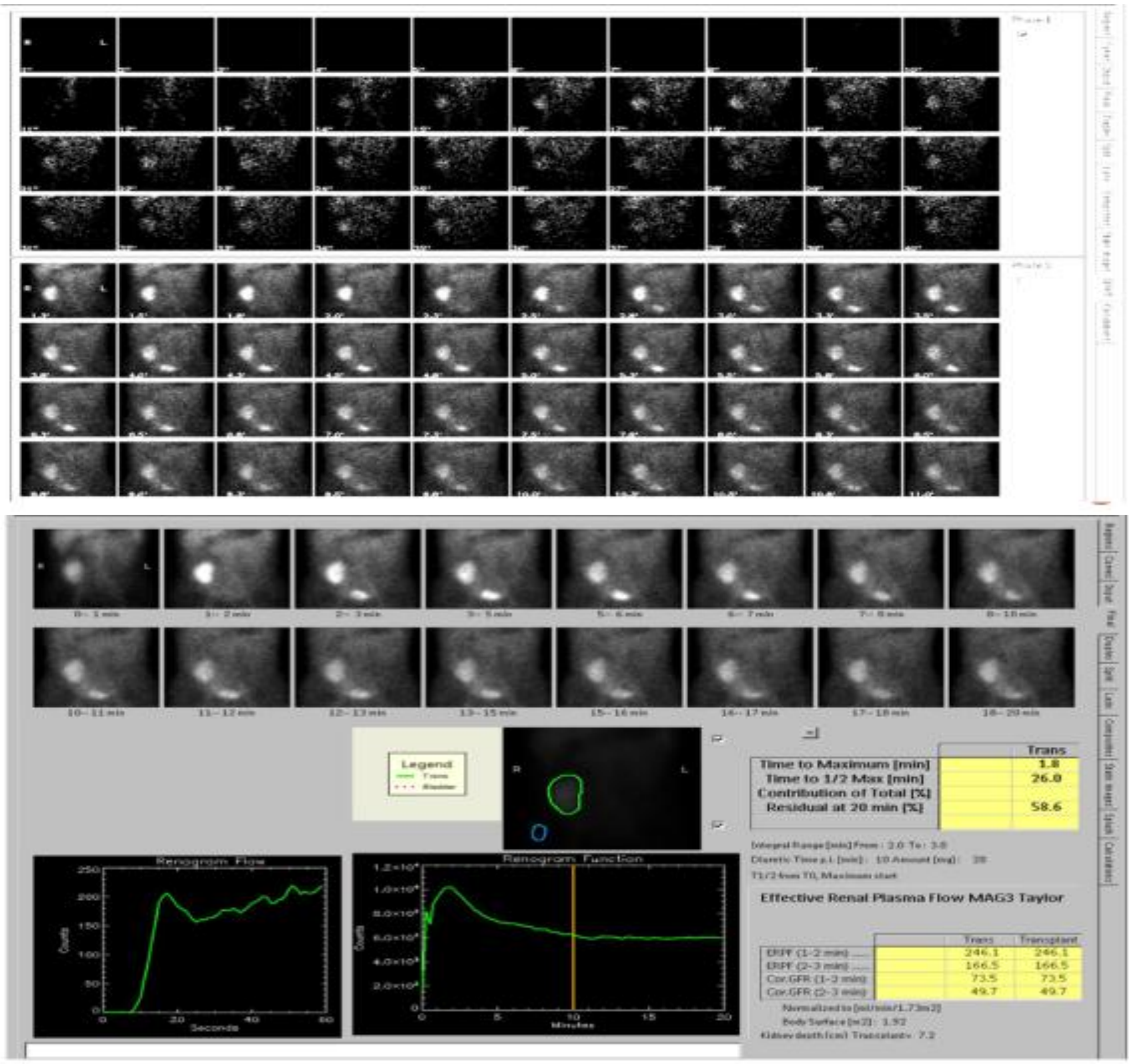

Figure (2): Using ^{99m}Tc-DTPA, a patient with acute tubular necrosis had a renal scintigraphic examination. Phase of flow (A). Take note of the graft's typical flow. Phase (B) is functional. The radiopharmaceutical's concentration and excretion have decreased somewhat, and the radiotracer's accumulation has been slightly reduced.

When both diagnostic features were identified, a combined pattern was diagnosed as combined ATN and acute rejection (12 cases) (Figure 3). Statistically, there was a significant difference between the three groups regarding excretion due to parenchymal retention, due to calyceal retention, and reduced due to both parenchymal and caliceal retention. The renal isotope parameters were displayed in **Table 2**.

Table (2): The diuretic renogram parameter were illustrated in each group.

Diuretic Renography (DR) Parameters		(AR) N=16	Combined (AR) & (ATN) N=12	(ATN) N=28	Test of significance
Perfusion	**Reduced**	16 (100%)	12 (100%)	23 (82.1%)	MC=5.49, P=0.064
	Good	0 (0%)	0 (0%)	5 (17.9%)	MC=5.49, P=0.064
Uptake	**Reduced**	16 (100%)	12 (100%)	23 (82.1%)	MC=5.49, P=0.064
	Good	0 (0%)	0 (0%)	5 (17.9%)	MC=5.49, P=0.064
Excretion	**Decreased due to parenchymal retention**	3 (18.8%)	2 (16.7%)	19 (67.9%)	MC=38.99, P<0.001*
	Decreased due to calyceal retention	13 (81.2%)	2 (16.7%)	3 (10.7%)	MC=38.99 P<0.001*
	Reduced to both	0 (0%)	7 (58.3%)	4 (14.3%)	MC=38.99, P<0.001*
	Good excretion	0 (0%)	1 (8.3%)	2 (7.1%)	MC=38.99, P<0.001*
T1/2 (min)		18.19 ± 4.4	17.08 ± 4.58	19.61 ± 4.97	F=1.31, P=0.280
GFR (ml/min)		63.81 ± 13.32	48.75 ± 6.36	56.5 ± 11.46	F=6.24, P=0.004*

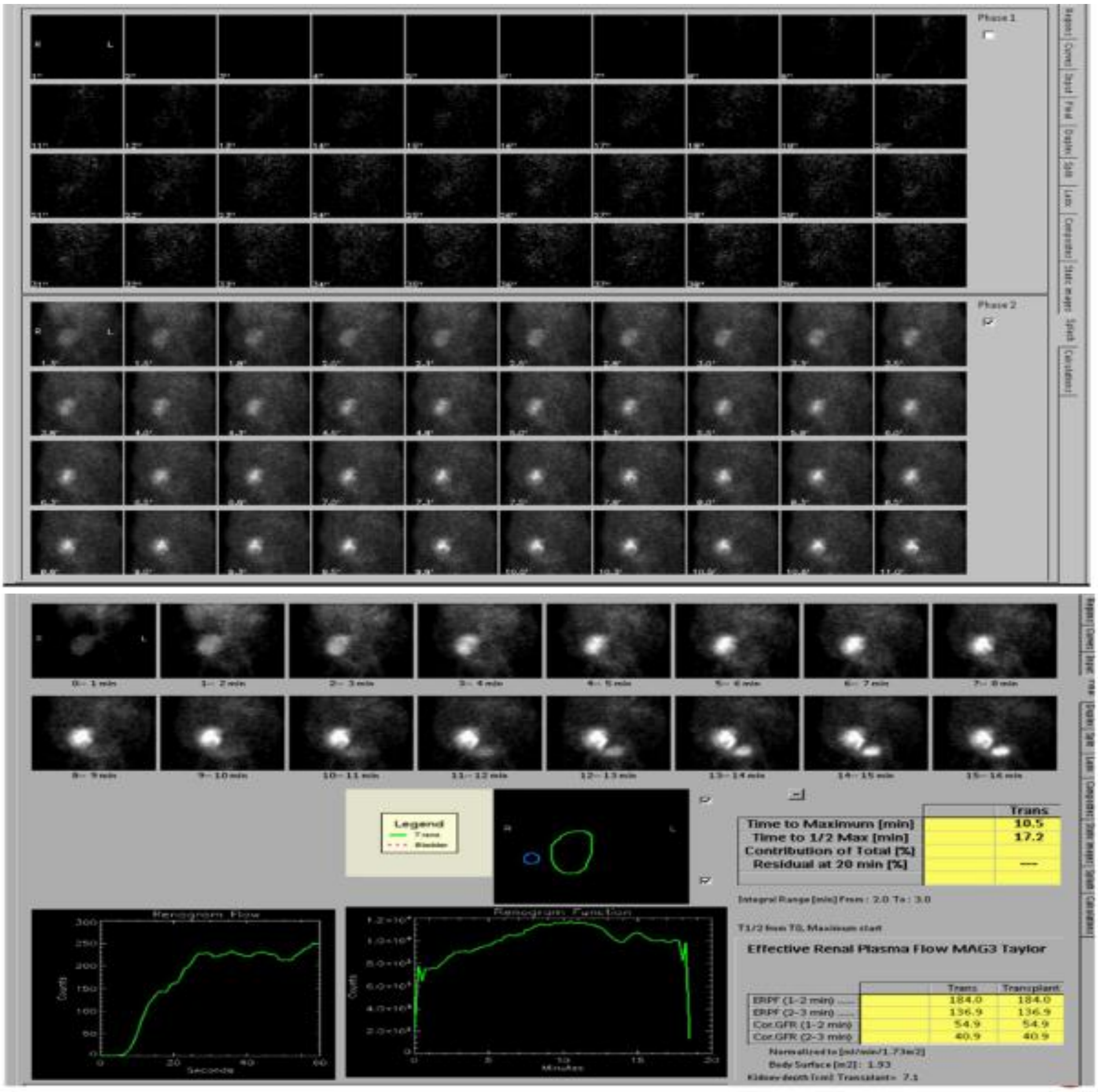

Figure (3): Using ^{99m}Tc-DTPA, a patient with acute tubular necrosis and acute rejection had a renal scintigraphic examination. Phase of flow (A). Take note of the significant drop in flow to the graft. Phase (B) is functional. The radiotracer's concentration, accumulation, and excretion are all somewhat decreased.

There was an excellent agreement between both radiologists regarding the interpretation of the isotopic findings in the diagnosis of acute rejection, ATN and combined acute rejection with ATN in cases kappa= 96.4 as shown in **Table 3**.

Table (3): Agreement between first and second observers

Variable	Radiology 1 (N= 26)	Radiology 2 (N = 56)	Kappa Agreement (95% CI)	% Agreement
Rejection	16	17	0.944 (0.869-1.0)	96.4
Acute Tubular Necrosis & Acute Rejection	14	14		
Acute tubular necrosis	26	25		

The total accuracy for both radiologists regarding the final diagnosis by using the pathology as the gold standard was over 90% in each group, except for radiology number two for the diagnosis of combined ATN and rejection patients, which was 89.3% as shown in **Table 4**.

Table (4): Validity of radiological findings in diagnosing studied lesions

	Variable	TP	TN	Sensitivity %	Specificity%	PPV%	NPV%	Accuracy%
Radiology 1	Rejection	15	39	93.8	97.5	93.8	97.8	96.4
	ATN & Rejection	11	41	91.7	93.2	78.6	97.6	92.8
	ATN	25	27	89.3	96.4	96.2	90.0	92.8
Radiology 2	Rejection	15	38	93.8	95.0	88.2	97.4	94.6
	ATN & Rejection	10	40	83.3	90.9	71.4	95.2	89.3
	ATN	24	27	85.7	96.4	96.0	87.1	91.1

DISCUSSION

Although immunosuppressants are used effectively, acute rejection still poses a serious hazard for recipients of renal allografts. In our study the incidence of acute rejection post renal transplantation was 28%, and this result is consistent with **Aktaş *et al.*** [(12)] study, in which the incidence of allograft dysfunction related to acute rejection occurs in 30% to 40% of patients. Our study states that there is a male predominance in affection (92.9%).

Acute tubular necrosis is more likely to develop early in the course of a problem than acute rejection, according to our study. This is explained by prolonged ischemia (cold or warm) and reperfusion damage, which may resolve on its own over the course of the first two weeks [(4)]. Acute tubular necrosis is the most common cause of "delayed graft function," which necessitates dialysis in the first week after transplantation [(13)]. Our study demonstrated the most powerful significant parameter is delayed excretion ($P<0.001$), either because of parenchymal retention of the tracer due to damaged tubules as in cases of ATN or because of calyceal retention of the tracer as in cases of acute rejection due to activated T cell activity. If retention of the tracer is hindered in both parenchyma and calyces, the combined pathologies are suspected, and this copes with **Sanches *et al.*** study at 2003 [(14)].

Additionally, changes in perfusion may play an additional significant role in differentiation between both entities; whereas a reduction in perfusion is almost a common finding in cases of acute rejection, it may be evident in a few cases of ATN, and this is in agreement with **Sanches *et al.*** study at 2003 [(14)].

In our study, the accuracy of diuretic renography in diagnosis of acute tubular necrosis and acute rejection is 92.8% and 96.4% respectively however, in diagnosis of combined of both elements is 89.3% and this coincides with the previous studies [(14)]. So, it is the preferred method over invasive needle biopsy as it has less complication, cost, and patient morbidity. There is strong agreement between both readers in our study (96.4%), which is higher than previous studies [(2,12)].

The limitation of our study was the small number of cases and lack of other radiological modalities in comparison.

CONCLUSION

Dynamic 99mTc-DTPA imaging is a non-invasive method for accurate diagnosis of medical allograft renal transplant complication, in addition to the onset of graft dysfunction and the clinical status of the patient. Diuretic renography can differentiate between acute allograft rejection and acute tubular necrosis with higher sensitivity and specificity.

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