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# RENAL ALLOGRAFT ACCUMULATION OF TECHNETIUM-99M SULFUR COLLOID AS A PREDICTOR OF GRAFT REJECTION

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## ABSTRACT

A perplexing issue in diagnosing the cause of renal allograft dysfunction is differentiation between rejection—the most common cause—and many other possibilities that have detrimental effects on graft function. This study was designed to determine whether technetium - 99m sulfur colloid (TSC) accumulation could predict graft rejection. We prospectively studied 54 episodes of allograft dysfunction in 53 kidney transplant recipients who had undergone TSC scintiscanning and graft biopsy, within one week of evidence of allograft dysfunction.

Visual analysis of TSC uptake was done by comparing allograft uptake with that of the fifth lumbar vertebra (L5) marrow. A 3+ result meant that allograft uptake was greater than L5 marrow uptake; 2+, allograft uptake was the same as L5 marrow uptake; 1+, less than and 0, no allograft uptake. Transplant accumulation of ≥2+ was considered consistent with rejection ($p$=0.01). Allotransplant biopsies were interpreted based on the Banff Working Classification and rejection was noted in 45 of 54 renal biopsies. 42 of 45 biopsy - proven rejection episodes had ≥2+ graft uptake.

This nuclear medicine technique has a sensitivity of 93.3%, specificity of 44.4%, a positive predictive value of 89.3%, a negative value of 57.1% and an efficiency of 83.3% in the diagnosis of renal allograft rejection.

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**Keywords**: Kidney transplantation, Allograft dysfunction, Rejection, Technetium-99m sulfur colloid.

## INTRODUCTION

Since the first successful kidney transplantation performed in 1954, various fields of transplantation have made tremendous progress.[1-3] Despite these improvements, many complications occur following renal transplantation, and immunological complications are still the leading cause of graft loss. [2-4] Differentiation between rejection and many other causes of allograft dysfunction remains a diagnostic challenge that is best done by graft biopsy, and biopsy has disadvantages such as risk of bleeding or infection,

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**Table I. Final diagnoses in 54 episodes of allograft dysfunction and the time after transplantation at which each had occurred.**

| Final diagnosis | Number of episodes | Time between Tx & dysfunction | |
|---|---|---|---|
| | | Mean ±SD | Range |
| Acute cellular rejection | 26 | 90.7 ±20.4 | 5 to 1095 days |
| Acute vascular rejection | 6 | 6.2 ±2.8 | 1 to 10 days |
| Chronic rejection | 11 | 34.5 ±15.4 | 18 to 72 months |
| Acute on chronic rejection | 2 | 32.5 ±23.3 | 16 to 49months |
| ATN | 6 | 6.6 ±4.9 | 1 to 14 days |
| Recurrence of FSGS | 1 | 6 months | 6 months |
| CMV infection | 1 | 14 days | 14 days |
| Transplant glomerulopathy | 1 | 18 months | 18 months |
| Total | 54 | Mean ISD | |

considerable cost, and need for hospitalization.[5,6] Nuclear medicine techniques provide a non-invasive, outpatient and less-costly alternative to evaluate renal allograft rejection.[1,4] Since the early 1970s, several investigators have studied various radiotracers that might accumulate in rejecting grafts such as $^{67}$Ga citrate, $^{125}$I-fibrinogen, $^{111}$In-labeled white blood cells and $^{99m}$Tc sulfur colloid (TSC) in order to predict renal allograft rejection.[7] For reasons of reliable graft visualization and physiologic properties (e.g. rapid blood clearance), to date TSC is accepted as the agent of choice for evaluation of rejection.[7] Although several studies have been conducted to assess the accuracy of renal allograft TSC accumulation in the diagnosis of rejection, most have defect regarding lack of biopsy proof.

The goal of the current study was evaluation of the usefulness of graft TSC accumulation in predicting renal allograft rejection by means of comparing this imaging procedure with biopsy as the "gold standard".

## PATIENTS AND METHODS

### Patient population

Between May 1995 and December 1997, 57 episodes of renal allograft dysfunction occurring in 55 transplant recipients were studied prospectively at Shahid Labafinejad and Baghiyatollah Medical Centers. Patients who had undergone TSC scintiscanning and graft biopsy within one week of allograft dysfunction were included in the study. Coincidence of acute tubular necrosis (ATN) and acute rejection was seen in two patients and one patient had graft vascular occlusion (Doppler: Resistive Increment=100%). These 3 episodes were excluded due to impossibility of interpreting TSC uptake in the rejected graft and the remaining 54 episodes in 53 recipients were entered in the study. Renal allograft dysfunction was defined as: 1) a 20% or greater increase in serum creatinine from previous normal value, or 2) failure of pretransplant serum creatinine to decline by more than 0.75 mg/dL/24h to a baseline of 2.5 mg/dL or less during the immediate postoperative period (1 to 14 days). Patients had received transplants from live related (n=3) and non-related (n=50) donors. Six patients had retransplant kidneys. The majority of patients received triple immunosuppressive therapy with prednisone, cyclosporine and azathioprine (n=30) while some received only prednisone and cyclosporine (n=23). In 40 patients with allograft dysfunction in whom acute rejection was highly suspected based on the clinical and laboratory data, treatment was begun with intravenous pulse methylprednisolone therapy, 20 mg/kg (maximum 1.0 g). Biopsy-proven acute rejection episodes unresponsive to steroid pulse were treated with ALG 10-15 mg/kg/24h for 7 to 10 days (n=11). Three patients with a pathologic diagnosis of acute vascular rejection were treated with plasmapheresis. No patient was on heparin therapy, nor were TSC scintigrams obtained within three days of transplantation or pulse therapy.

### Imaging technique

20-30 minutes after the intravenous administration of 2 mCi of TSC, patients were imaged for 10 minutes using a large field of view gamma camera with a low-energy all-purpose collimator. Analogue images were acquired for all patients. Next, patients received 15 mCi of DTPA with performance of flow study (1 sec/frame for 60 sec) and standard renograms (1 min/frame for 27 min). All doses in children were adjusted for body weight. Through DTPA perfusion scan, excretion and drainage were evaluated. Visual analysis of TSC scintigrams were done by a specialist blinded to clinical and histopathologic data by comparing allograft uptake of radiocolloid with that of the fifth lumbar vertebra (L5) marrow uptake: 3+, allograft with greater than L5 marrow uptake; 2+, same as; 1+, less than and 0, no allograft uptake. Allograft accumulation of equal to or greater than 2+ was considered consistent with rejection.



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**Table II. Nuclear evaluation.**

| Final diagnosis | Graft TSC uptake | | DTPA renogram | | | |
|---|---|---|---|---|---|---|
| | | | Perfusion | | Excretory function | |
| | <2+ | ≥2+ | acceptable | impaired | on time | delayed |
| Acute cellular rejection | 2 | 24 | 0 | 26 | 5 | 21 |
| Acute vascular rejection | 1 | 5 | 0 | 6 | 0 | 6 |
| Chronic rejection | 0 | 11 | 0 | 11 | 2 | 9 |
| Acute on chronic rejection | 0 | 2 | 0 | 2 | 0 | 2 |
| Acute tubular necrosis | 4 | 2 | 1 | 5 | 0 | 6 |
| Recurrence of FSGS | 0 | 1 | 0 | 1 | 0 | 1 |
| CMV infection | 0 | 1 | 0 | 1 | 1 | 0 |
| Transplant glomerulopathy | 0 | 1 | 0 | 1 | 0 | 1 |

**Table III. Histologic grading in 45 episodes of rejection.**

| Histology | Borderline changes | Grade I | Grade II | Grade III |
|---|---|---|---|---|
| Acute cellular rejection | 6 | 10 | 10 | 0 |
| Acute vascular rejection | 0 | 1 | 4 | 1 |
| Chronic rejection | 0 | 4 | 7 | 0 |

**Table IV. Comparison of biopsy with allograft TSC accumulation.**

| Biopsy | Renal allograft TSC uptake | |
|---|---|---|
| | <2+ | ≥2+ |
| Rejection | 3 | 42* |
| No rejection | 4 | 5 |

*$p$= 0.01, Fisher's exact test.

### Biopsy technique

Allograft biopsies were performed using a Tru-cut needle on 57 occasions in 55 patients. Except for hematoma in one patient, no other complication occurred. Indications for allograft biopsy were absence of hydronephrosis in ultrasonography and one of the following: 1) acute allograft dysfunction in association with new-onset oliguria (<0.4 L/24h), 2) failure of serum creatinine to stabilize or decrease within 3 days of institution of antirejection therapy, 3) when ATN or pre-renal etiology was suspected clinically, 4) when allograft function did not improve upon correction of a single etiologic factor, and 5) when recurrence of primary disease in graft is suspected. All specimens were examined by a renal pathologist according to the Banff Working Classification for transplant kidney pathology.[12]

Final diagnosis of the cause of allograft dysfunction was based upon a combination of clinical and laboratory criteria (including blood cyclosporine level) and response to specific treatment with pathologic confirmation.

### Statistical analysis

Statistical analysis was performed using a microcomputer software program, SPSS for MS WINDOWS Release 6.0. Two-tail Fisher's exact test was used to compare categorial data.

## RESULTS

The 54 renal allograft dysfunction episodes in the study occurred in 53 recipients, with one patient having two separate episodes. The mean age (±SD) of patients was 30±11 years. 40 patients were male (75.5%) and 13 were female (24.5%).

Table I outlines biopsy-proven episodes and the time after transplantation at which each pathology has occurred. Of 45 confirmed rejection episodes, 42 had ≥2+ allograft accumulation (Table II). Table III shows histologic grading of rejection according to the Banff Working Classification. Compared with the renal allograft biopsy, TSC accumulation has a sensitivity of 93.3%, specificity of 44.4%, a positive predictive value of 89.3%, a negative predictive value of 57.1% and efficiency of 83.3% (Table IV). Our study indicates that transplant TSC accumulation of ≥ 2+ is predictive of allograft rejection ($p$=0.01).



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## DISCUSSION

The most common cause of renal allograft dysfunction is rejection[3,4] There are many disorders which have detrimental effects on graft function (e.g. ATN, cyclosporine nephrotoxicity, recurrence of native disease, etc.) and rejection, and acute rejection should be differentiated from among these possibilities.[3,5] Although renal biopsy has remained the definitive means to establish the diagnosis of rejection, there is little question that a non-invasive technique that can help distinguish between rejection and other causes of transplant failure is highly desirable.[4-6]

Since the early 1970s, several investigators have studied various radiotracers to predict allograft rejection, and TSC was accepted as the agent of choice.[4,7] Imaging with TSC is based on trapping sulfur colloid particles in fibrin thrombi present in the rejecting graft. Since transplants with ATN have good blood flow without thrombi formation, theoretically this method should separate these two entities,[1] but practically conflicting data from several studies exist.[6-10] George et al. evaluated renal allografts by visual scintigraphic quantitation of TSC and found that accumulation was marked in chronic rejection, slight in acute rejection and absent in normally functioning transplants or in those with ATN.[8] On the other hand Frick et al. observed TSC accumulation in 89% of transplants with rejection, 30% with ATN and 30% with sepsis.[9] Kim et al. found that by grading the degree of radiocolloid accumulation within renal allografts in comparison with pelvic marrow uptake, the specificity of the technique was improved.[10] Later George etal. compared visual evaluation with computer quantitation of TSC accumulation, with collection of >50% as compared with the iliac crest marrow being consistent with rejection. Computer quantitation resulted in improvement of sensitivity from 78% to 95% and specificity from 83% to 100%. This method was also able to correct false-positive readings in ATN and sepsis.[11] Comparison of these studies is difficult, because of different methodologies, differing scales to quantitate TSC accumulation, and differing criteria for establishing rejection. False-positive results in visual analysis have been reported in the first 3 days after transplantation, in patients on high dose steroid therapy, infections, congestive heart failure and occasionally ATN.[1,10]

In the current study, ≥2+ TSC uptake was seen in 88.4% of transplants with acute rejection (n=26), 100% with chronic rejection (n=11) and 100% with acute on chronic rejections (n=2). In contrast to George et al., our study demonstrated prominent TSC accumulation in acute rejection. Three false-negatives in our study were seen in two transplants with acute cellular (grade I,II) and one with grade II acute vascular rejection and all had received steroid pulse therapy before scintiscanning and had moderate to severely impaired perfusion on DTPA renogram. Five false -positives in the study were seen, 2 in transplants with ATN, one with cytomegalovirus infection (confirmed by a 4-fold rise in antibody titer and absence of ATN and rejection in histologic exam), one with transplant glomerulopathy and one with recurrence of focal and segmental glomerulosclerosis. Both recipients with ATN and ≥ 2+ TSC uptake had minimally impaired graft perfusion and received steroid pulse therapy based on clinical impression of rejection prior to TSC scintigraphy. TSC uptake may increase in non-rejecting grafts up to 3 days after steroid pulse therapy.[11] None of the TSC scintiscannings in the study were done during this period.

The important aspect of this study is biopsy proof in diagnosis of the cause of allograft dysfunction. Except for Massengill et al., none of the other investigators have used biopsy to establish the diagnosis of rejection.

TSC imaging is a noninvasive outpatient procedure with little radiation and no complication. Also, its accumulation is not renal function-dependent and thus is unaffected by cyclosporine.[4]

TSC scintiscanning was a good indicator of both acute and chronic rejection in the vast majority of our patients. It's use can therefore more appropriately diagnose renal allograft dysfunction in kidney transplant patients.

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