

ROLE OF IMAGING IN RENAL TRANSPLANT COMPLICATIONS - A HOSPITAL BASED STUDY

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ABSTRACT

Background: Thirty five thousands patients receive renal transplants every year world wide. This study was conducted to determine and evaluate the diagnostic role and accuracy of Ultrasonography including Doppler analysis and Radionuclide Scanning in patients with renal transplant complications.

Subjects and Methods: It was an observational study. Cases were collected from AFIU, MH and Jinnah Memorial Hospital Rawalpindi. Ultrasound and Doppler analyses were done in the Radiology Department of CMH Rawalpindi. Renal isotope scans were performed at NMC Rawalpindi. A total number of 52 patients were studied. Male female ratio was 42 to 10 (80.8% to 19.2%). The post-transplant duration was 02 days to 06 years.

Result: The most frequent complications were peri-transplant fluid collection (27%), followed by rejection of transplant (25%) and cyclosporine nephrotoxicity (11.54%). Other complications which were also observed were Acute Tubular Necrosis (7.69%) and hydronephrosis (15.4%).

Conclusion: Ultrasound is excellent modality to evaluate location, volume and change in volume of Perinephric fluid collection. Radionuclide imaging detects altered or diminished renal function due to acute tubular necrosis, rejection of transplant and toxicity from medications. Radionuclide imaging is most useful modality for assessing renal function. Standard for evaluating vascular complications is angiography, however duplex Doppler ultrasound is an excellent non invasive method for screening. Other transplant complications like abnormalities of collecting system and renal parenchyma are well evaluated by both ultrasound and radionuclide imaging.

Keywords: Renal transplant complications, doppler, radionuclide scanning, renal isotope scanning, renal transplant rejection, cyclosporine nephrotoxicity.

INTRODUCTION

In the space of little more than 30 years, renal transplantation has progressed from an essentially unsuccessful experimental procedure conducted in the isolation of a small number of pioneering medical research centers to a wide spread and routine

procedure for an estimated 35,000 patients worldwide each year. Indeed the transplant recipients of today are indebted to the courage of renal transplant recipients of the 1950s and 1960s, as well as to the vision and perseverance of those who treated them.

Despite providing the best quality of life and the most cost effective treatment option for end stage renal disease, renal transplantation remains at the challenging and exciting interface between clinical

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research and laboratory science. Its development has also been the catalyst for transplantation of other solid organs, the practice of immunosuppression and much of clinical immunology. Nevertheless, failures, both acute and long term, continue to serve as a salutary reminder of our incomplete understanding and control of the human immune system.

The post-transplant decrease in renal functions often appears nonspecific at first and may be the result of medical complications, urologic complications, or a combination of these. The clinical presentation of increasing serum urea and creatinine, fever, and tenderness in a renal transplant patient is nonspecific as to its causative factor. In many instances, it is the imaging procedure that helps triage these patients into the appropriate group of post-transplant complications. The correct diagnosis directs the correct therapy.

Sonography provides rapid and safe assessment of renal allograft anatomy. Duplex sonography allows the simultaneous sonographic imaging of the transplant, with Doppler assessment of vascular flow. Intrarenal arterial Doppler sonography is used as a valuable tool in noninvasive monitoring of transplant kidneys[1]. Doppler analysis improves the diagnostic accuracy for these patients [2], an abnormal sonogram is highly predictive of acute transplant rejection but a normal sonogram does not exclude the possibility of rejection [3].

There are two major agents used in the nuclear medicine (NM) examination of the renal allograft. Technetium-99^m DTPA renography evaluates flow of agent into the kidney and its drainage from the collecting system into the bladder. Significant blush in the transplant occurs within 6 seconds of the visualization of the ipsilateral iliac artery. Within 2 minutes, the renal cortex reaches peak activity, followed by a progressive decline in activity over the next 2 to 30

minutes. The bladder accumulates activity as the kidney activity declines. The second compound used is ^{99m}Tc-dimercaptosuccinate (DMSA). It gets fixed in the tubule cells at a very low extraction rate. Good images may be obtained 1-2 hours after injection. The normal renal image is formed by the functioning cortical tissue and corresponds well with the radiographic renal outline. This is an important consideration in the study of renal morphology.

Generally Computed tomography (CT) has no role in the routine evaluation of renal transplant. However CT scan with 3D-reconstruction of the data may show the anatomy of the transplant vessels and their relations.

Magnetic resonance imaging (MRI) is the latest addition to the armamentarium of diagnostic allograft evaluation. It has good image quality. Multiplanar imaging of the anatomy of the transplant is a big advantage MRI has over other modalities. MR angiography and MR urography are noninvasive diagnostic modalities with the potential to replace angiography and pyelography in the near future [4].

This study was designed to determine and evaluate the diagnostic role and accuracy of Ultrasonography (US) including Doppler analysis and Radionuclide Scanning in patients with renal transplant complications. It was an observational study. Comparison of these two modalities was also done in their diagnostic efficacy in renal transplant complications.

PATIENTS AND METHODS

Study was carried out at the Radiology department of Combined Military Hospital (CMH) Rawalpindi and Nuclear Medical Centre (NMC), affiliated with Armed Forces Institute of Pathology (AFIP). Patients of renal transplant were collected from Armed Forces Institute of Urology (AFIU), Military

Hospital (MH) Rawalpindi, and from Jinnah Memorial Hospital Rawalpindi.

Patients of all ages, both sex and all socioeconomic strata who presented with clinical and laboratory evidence of any renal transplant complication were studied. They were subjected to ultrasonography including Doppler analysis of the transplanted kidney and the feeding vessels, and then radionuclide scan (^{99m}Tc -DTPA) of the same patient was performed.

Doppler examinations were done at Radiology department of Combined Military Hospital Rawalpindi. Scans were done with color Doppler ultrasound machine, LOGIQ 500 by General Electronics Medical Systems. This machine bears probes of 3.5, 5 and 7.5 MHz of convex and linear configurations and is capable of performing the Power Doppler, Color Doppler and Pulse Doppler studies. In routine 5 MHz probe was used. Patients were assessed for renal size and shape, renal cortical echogenicity, corticomedullary differentiation, hydronephrosis present or not, perinephric or perivesical fluid collection, pattern of blood flow with measurement of resistive index (RI) in various intra-renal arteries, any turbulence of blood flow in renal arteries or veins, any pseudoaneurysm, any other renal abnormality detected by ultrasonogram like renal calculus, cyst, mass etc.

Nuclear scans were done at Nuclear Medical Center (NMC) Rawalpindi, which is incorporated with Armed Forces Institute of Pathology Rawalpindi. ^{99m}Tc was used as a radiotracer agent and DTPA as carrier. 10 mCi of radiopharmaceutical was injected as a compact bolus in a volume of 0.5-1 ml through a three-way stopcock and flushed with 10 ml of normal saline. All the images were acquired on Scintatronix gamma camera with low energy high-resolution general-purpose hole collimator with an on line computer. Gamma camera energy window width was set at $140 \text{ keV} \pm 20 \text{ keV}$ i.e. a range from 120-160 keV. Data was acquired on a

dedicated computer in 64×64 matrix as a dynamic sequential study with an initial frame rate of 1 frame per second for 30 seconds. It was followed by 60 frames of 30 seconds each. Total acquisition time was 30.5 min. Delayed views were acquired as and when required.

RESULTS

The study was carried out in 02 years i.e. January 2000 to January 2002. A total of 52 cases were studied. Age of the patients ranges from 18 years to 53 years. 38 patients (81%) were between 27-45 years. It includes 42(80.8%) males and 10(19.2%) females. Duration post-transplant (when the patient was examined) ranges from 02 days to 06 years.

Most of the early presentation was with rising urea level after renal transplant. Late presentation i.e. after one year of transplant was with easy fatigability or rising urea level on routine check up. One patient was subjected to the investigations because he was found to have increased echogenicity of the transplanted kidney on follow up ultrasound at 10 months post-transplant.

Various complications were observed in these patients depending upon the time post transplant and their clinical picture. These complications were evaluated in the light of clinical and laboratory data on presentation and clinical and laboratory response after the appropriate treatment.

Peri-transplant fluid collections were seen in 14(86.9%) patients. Hydronephrosis was observed in 08(15.4%) cases. Decreased renal functions with raised resistive index (RI) was seen in 22(44.3%) cases (table-1).

Rare complications like stones in transplanted kidney were seen in 06(11.54%) cases. Renal artery thrombosis was observed in 01(1.9%) patient.

Raised resistive index was the most common finding in the patients, who were

evaluated for some derangements in renal functions after transplant. It was seen in 22 cases in our study of 52 cases. Out of these 22 cases 12 later on proved to be due to rejection. ATN was seen in 04 and toxicity due to immunosuppressive drugs, e.g. cyclosporine was proven to be the cause in 06 patients (table-2).

Perinephric fluid collections are well evaluated with US. Radionuclide imaging is the most useful modality for assessing renal functions. Although the standard for evaluating vascular complications is angiography, US with Doppler is an excellent noninvasive method for screening vascular complications. Other transplant complications such as abnormalities of the collecting system and renal parenchyma are well evaluated with both radionuclide imaging and US.

DISCUSSION

End stage renal disease is a devastating physical, economical and social problem for the patients and their family. Renal allograft transplantation has become more and more commonplace in the treatment of renal failure. The major stimulus for these increasing numbers has been the introduction of cyclosporine and other effective measures of immunosuppression with significant increase in the survival of the transplanted kidney [5]. In the most ideal situation, 100% allograft survival is expected in sibling transplantation. Currently an 80% survival rate is expected in the first year for cadaveric transplants treated with cyclosporine immunosuppression.

The transplanted kidney is subject to two major groups of complications. They are [6,7], medical complications e.g. rejection, acute tubular necrosis (ATN), immunosuppressive therapy toxicity and recurrent disease and surgical or urologic complications like perinephric fluid collections, obstruction to the draining ureter and occlusion of transplant

blood supply. According to the time period these can be divided as shown in (table-3).

Postoperative fluid collections are common following transplantation seen in about 26.9% of cases in our study. This fluid collection could be hematomas, urinomas, abscesses or lymphoceles. The appearance and complications of a fluid collection depend on its composition as well as its location. Small crescentic peritransplant fluid collections seen immediately after transplantation are most likely hematomas or seromas and should be considered a normal sequela of surgery [8]. Size, location, and growth determine the significance of these collections. Because an increase in size may indicate the need for surgical intervention, the size of any such collections should be documented on the baseline US. The appearance of peritransplant fluid collections is nonspecific, but using percutaneous aspiration of the fluid can make the diagnosis.

Urine leaks are relatively rare complications following transplantation and manifest in the early postoperative period with pain, swelling, and discharge from the wound. These leaks are related to surgical technique or distal ureteral necrosis. The appearance of urinomas is nonspecific on US images [8]. Radionuclide imaging studies will show progressive radiotracer activity in the abnormal collection, definitively demonstrating that the fluid is urine [9]. Another important type of peri-transplant fluid collection is lymphocele. These are usually discovered incidentally, are asymptomatic, and do not require therapy. On radionuclide images, a large photopenic region can be seen to exert a mass effect on the transplant. Symptomatic peritransplant fluid collections can be drained percutaneously under USG guidance.

Causes of diminished renal function include acute tubular necrosis, rejection (hyperacute, acute, and chronic), and drug nephrotoxicity. Acute tubular necrosis is the most common cause of "delayed graft

function", which is defined as the need for dialysis in the first week following transplantation [10]. Its causes include prolonged ischemia (cold or warm) and reperfusion injury. Theoretically, kidneys can be stored for 48 hours at 4° C following perfusion, but cold ischemia times of more than 24–30 hours result in a higher frequency of acute tubular necrosis [11]. With radionuclide imaging, the most conspicuous findings are delayed transit with delayed time to maximal activity (T-max), delayed time from maximum to one-half maximal activity (T-1/2), and a high 20 to 3 minute ratio. On sequential images, marked parenchymal retention is seen [9].

Rejection is seen in about 25% cases in our study. Acute rejection is relatively common following transplantation, with up to 50% of patients experiencing at least one episode in the first year. Patients may present with malaise, fever, weight gain, or a painful kidney. However, patients receiving cyclosporine may be asymptomatic [11]. The radionuclide imaging findings of acute rejections are characterized by diminished flow [9]. These findings are similar to those of acute tubular necrosis, and the two entities can be differentiated by the time course of the findings. Acute rejection rarely develops in the first few days after transplantation and instead will manifest with a decrease in function on serial radionuclide imaging studies. Thus, obtaining a baseline scan is extremely important. Chronic rejection is the most common cause of late graft loss. A graft with chronic rejection will have a thin cortex and mild hydronephrosis on both gray-scale US and radionuclide images. Chronic rejection is characterized by diminished uptake of radiopharmaceuticals [9] and also by normal parenchymal transit with absent or minimal cortical retention. When chronic rejection is advanced, there may be parenchymal retention of radiotracer [9]. A young lady of 29 years of age developed transplant failure on 3rd post op day. On ultrasound examination, the transplant was

swollen with raised resistive index. A big fluid collection was seen at the lower pole of the transplanted kidney. On exploration, hematoma was found along with a large tear in the transplanted kidney. Tear was repaired with fascia lata, but no renal functions were obtained. Nephrectomy had to be done on 16th post op day. On operation, another tear was found in the kidney, which indicates swelling of the kidney. Histopathology report showed it to be a case of acute rejection.

Drug nephrotoxicity is another cause of diminished renal function. In our study, it has been observed in 6 / 52 (11.54%) cases. Cyclosporine has the greatest nephrotoxic potential, with its vasoconstrictive effect on the afferent glomerular arterioles [11]. On radionuclide images, acute cyclosporine toxicity resembles mild acute rejection, with depressed effective renal plasma flow and parenchymal retention. Patients with a toxic reaction to cyclosporine have radionuclide imaging findings similar to those of chronic rejection [9]. Findings should be correlated with cyclosporine levels. In the short term, nephrotoxicity from cyclosporine is dose dependent and responds to a reduction in dosage [11].

US findings of diminished renal function include renal enlargement, increased cortical thickness, increased or decreased echogenicity of the renal cortex, loss of corticomedullary differentiation, prominent pyramids, collecting system thickening, and effacement of the central sinus echo complex. However, gray-scale US findings are subjective, and the negative predictive values vary between 17% and 50%. Although duplex Doppler US has not proved to be as accurate in the evaluation of transplant rejection as initially thought, most groups now use an elevated resistive index (> 0.8) as a nonspecific parameter of renal transplant dysfunction; reversal of diastolic flow may also be seen in rare cases. However, reversed diastolic flow is a non-specific, poor prognostic sign, and nephrectomy may be needed ultimately [12]. Causes of raised

resistive index are summarized in (table-4). Color Doppler sonography is insensitive in revealing and in allowing radiologists to differentiate the causes of graft dysfunction. However, Power Doppler sonography allows a prediction of the functional recovery of the graft at 12 months after transplantation not provided by resistive index levels [13]. Differentiation among acute tubular necrosis, acute interstitial rejection, acute cellular rejection, chronic rejection, and cyclosporine toxicity is usually made by using percutaneous US guided biopsy and cyclosporine levels.

Percutaneous biopsy is an invaluable diagnostic tool in transplant recipients with diminished renal function [14]. When US is

diagnosis of vascular complications, US

Table-1: Percentage of renal transplant complications

Complication	No. of Patients	% age of total
Peri-transplant fluid collection	14	26.9%
Hydronephrosis	08	15.4%
Raised resistive index (RI)	22	43.2%
Renal artery thrombosis	01	1.9%

Table-2: Differential of the causes of raised resistive index

	No of cases	Percentage of raised RI n=22	% age of total cases n=52
Transplant rejection	12	56.52%	25%
ATN	04	17.39%	7.69%
Cyclosporine toxicity	06	26.09%	11.54%

Table-3: Renal Transplant complications

	Immediate (<1 week)	Early (1-4 weeks)	Late (>1 month)
			Acute Rejection Chronic Rejection
Parenchymal	Acute Tubular Necrosis Rejection · Hyperacute · Accelerated Acute · Acute	Acute Rejection	Cyclosporine Toxicity Disease Recurrence Infection
Vascular	Renal Vein Thrombosis Renal Artery Thrombosis	Renal Vein Thrombosis	Renal Artery Stenosis
Urologic	Ureteral Oedema	Urinary Fistulae Urinoma	Ureteral Strictures
Fluid Collections	Haematoma Abscess	Urinoma	Lymphocoele Skin
Neoplastic	--	--	Malignancies Lymphomas
Iatrogenic	Post Biopsy Haemorrhage Renal AV Fistula Pseudoaneurysm	--	--

used to guide the needle, it improves the diagnostic yield of each needle pass. Unfortunately in our study none of the patient was subjected to this gold standard investigation, as this was not requested by the treating physician/nephrologists.

Vascular complications are an important cause of graft dysfunction [15], having high morbidity and mortality. Although angiography remains the standard for

Table-4: Causes of elevated resistive index

Parenchymal	Acute Rejection Acute Tubular Necrosis Pyelonephritis
Vascular	Renal Vein Thrombosis Hypotension
Urological	Ureteral Obstruction
Technical	Graft Compression

performed with duplex and a color Doppler mode is an excellent noninvasive modality for evaluating the affected vessels [8, 16]. Duplex

Doppler US is a useful, noninvasive, and portable initial procedure with which to screen patients for vascular complications of renal transplantation [17]. It has a sensitivity of 94.1% and specificity of 86.7% in the diagnosis of transplant renal artery stenosis [14]. Radionuclide can also be used to image vascular complications. Renal vein thrombosis is rarely a cause of transplant dysfunction. It occurs within the first week after transplantation [18] and is manifested clinically by sudden oliguria, graft tenderness, and swelling and transplant nephrectomy is usually performed to prevent infection [19]. On gray-scale US images, the allograft may appear swollen and hypoechoic. At Doppler US examination, venous flow is absent, and the arterial waveform shows reversed, plateauing diastolic flow [20]. Although reversal of diastolic flow is nonspecific (it is also seen in severe rejection and acute tubular necrosis), the combination of this waveform with absent venous flow is virtually diagnostic of renal vein thrombosis [21].

Renal artery thrombosis is a rare complication of transplantation that occurs soon in the early postoperative period and almost invariably leads to graft loss. Associated findings include severe rejection, severe tubular necrosis, and faulty surgical anastomosis [22]. We had one unfortunate patient of renal artery thrombosis. This young man of 30 years did not achieve renal functions in post operative period. Ultrasound and Doppler analysis was done which failed to show the renal transplant even. Radio-isotope scan was done, which showed a defect in the right iliac fossa region. Possibility of renal artery thrombosis was given. On exploration, transplanted kidney was small and necrosed and the renal artery was found to be thrombosed. Transplant nephrectomy was done. Renal artery thrombosis is also diagnosed on US with duplex and color Doppler techniques which fail to demonstrate intrarenal venous and arterial flow. However, because these

findings may mimic those of severe rejection, angiography may be warranted in problem cases [19].

Dilatation of the pelvicalyceal system of the transplanted kidney is a non-specific finding and it was seen in 8/52 i.e. 15.4% of our cases. This is rarely obstructive in nature in these patients. More complete hilar dissections in recipients of grafts from live donors may explain the greater frequency of urinary tract complications following transplantation. US will demonstrate dilated calices, although this is a nonspecific finding because it is also seen in cases of diminished ureteral tone resulting from denervation of the transplant [8]. The utility of Doppler US assessment of resistance and pulsatility in the setting of urinary tract obstruction after transplantation has been evaluated but has not yet been determined [8,23]. Treatment of urinary tract obstruction consists of stent placement, balloon dilatation, or correction of the source of extrinsic compression of the collecting system.

Ultrasound guided percutaneous interventional procedures can be safely used to diagnose and treat the urological complications of renal transplantation. They can obviate surgery, or may allow conservative therapy until the condition of the patient is optimized for surgical intervention [24].

It can be concluded that renal transplantation has changed the outlook of patients with end stage renal disease, and has emerged as the most suitable method of treatment. Following renal transplantation, patients are often evaluated with ultrasonography or radionuclide imaging to assess renal function and the presence of possible complications. Both modalities are inexpensive, noninvasive, and non-nephrotoxic. Given the prolonged survival now possible for renal transplant recipients, because of newer medical and surgical technologies, it is getting increasingly

important to use noninvasive methods of screening these patients and evaluating their symptoms or signs of complications.

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