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Pseudorejection and True Rejection after Kidney Transplantation: Classification and Clinical Significance

Key Words

Pseudorejection • True rejection • Kidney transplantation •
Hyperglycemia • Creatinine • Resistive index

Abstract

Objectives: Multiple factors may result in an elevation in serum creatinine level after kidney transplantation, mimicking rejection. It is crucial to differentiate between a true rejection and other conditions inducing a 'pseudorejection', in order to avoid overtreatment, or worse, mistreatment. Our goal was to review and classify true rejections and pseudorejections and their clinical significance. **Material and Methods:** This was a retrospective review of articles published in the USA and Europe, from 1976 to the present. The sites from which information was retrieved included PubMed, Clinical Imaging, Histopathology, Archives of Surgery, JACS, the American Urological Association, Medline and Springer Link. The importance of the resistive index will also be emphasized. **Results:** We reviewed 61 articles regarding the causes of renal graft dysfunction, which may be classified into true rejections and pseudorejections, the latter including the following 6 factors: hyperglycemia, ureteral obstruction, lymphocele, arterial stenosis, infection and recurrence of primary pathology. **Conclusions:** 'Pseudorejection' has been described only once, for the first time in 1976 in the USA, and

there have been no other reports since then. Multiple factors, mainly hyperglycemia, may induce a pseudorejection, presenting with an elevation of serum creatinine level and leading the clinician to an erroneous diagnosis of true rejection initially, resulting in inappropriate management.

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Introduction

An acute rejection of a transplanted kidney needs to be detected early in the postoperative course. Our armamentarium to identify such an episode seems to be acceptable, including the serum level of creatinine and an early Doppler ultrasound of the transplanted kidney; certainly, the final diagnosis will be confirmed by a biopsy of the transplanted kidney.

Serum creatinine level is recommended as one of the best measures of renal function with the greatest sensitivity and availability in the clinical setting and is used as the daily parameter of renal function on routine follow-up of transplanted patients.

When the serum creatinine level rises above 25% of its normal value, we have to start suspecting a rejection of the graft, requiring more investigation and additional treatment. On the other hand, a deteriorated kidney

Fig. 1. RI measurement.

function with increased creatinine can be due to other factors unrelated to graft rejection, and those factors should be identified as early as possible, in order to prevent unnecessary treatment that could be toxic and useless. The management of acute rejection starts with pulse steroids, and these medications can be associated with high mortality and morbidity [1–3].

Therefore, the objective of the present review was to present the causes of renal graft dysfunction, which may be classified into true rejections, including either vascular, parenchymal, urologic, infectious, neoplastic or iatrogenic origins, and pseudorejections, conditions in which a true rejection is suspected but is not the case, including the following 6 causes: hyperglycemia, ureteral obstruction, lymphocele, arterial stenosis, infection and recurrence of primary pathology.

Material and Methods

We initially reviewed articles published in the USA and Europe, from 1976 to the present, in order to identify factors inducing true rejection. The sites from which information was retrieved included PubMed, Medscape, Clinical Imaging, Histopathology, Urologia Internationalis, Archives of Surgery, JACS, the American Urological Association, BMJ, Medline and Springer Link.

When we encounter a rise in serum creatinine level after a kidney transplant, our diagnostic armamentarium includes a Doppler ultrasound of the transplanted kidney. It has the advantage of safely imaging the structure of the graft and its perfusion, without the need for intravenous contrast or ionizing radiation. We also

use the resistive index (RI), as described in the literature, as a main parameter. The RI is defined as shown in figure 1.

The RI is a widely used measure of resistance to arterial flow within the renal vascular bed and is calculated from the pulsed Doppler arterial waveform. An RI of less than 0.7–0.8 is considered normal, whereas an RI in excess of 0.9 is a strong indicator of transplant dysfunction. We reviewed the causes of elevated RI in the literature, by searching in Medscape, PubMed, Clinical Imaging, AUA and the Journal of Urology, Springer Link and Medline.

We finally searched in the literature for the most common conditions that are frequently associated with an elevated serum creatinine and in which rejection is suspected but is not the case. These conditions were described for the first and single time in 1976, in the USA, and were called ‘pseudorejection’ in a transplanted kidney. They include hyperglycemia, ureteral obstruction, infection, lymphocele, arterial stenosis and recurrence of the original disease. Each of these conditions will be discussed separately.

Results

Numerous factors play a role after a renal transplantation, leading sometimes to an unsuccessful postoperative course. It is of paramount importance to identify these factors and elucidate the reason why such incidents occur. Therefore, the causes of true renal graft rejection may be classified according to the timing following the operation. Furthermore, they can be classified as either vascular, parenchymal, urologic, infectious, neoplastic or iatrogenic. Accordingly, a classification of the causes of true renal graft rejection is shown in table 1.

Most of these events might present identically initially, with edema, systemic fluid overload and vascular issues. A Doppler ultrasound of the renal graft, as detailed before, would be very important. However, sometimes these conditions might have the same characteristics on ultrasound. An elevated RI above 0.9 is definitely a sign of renal dysfunction but is frequently not specific. Therefore, the value should be analyzed by integrating the clinical condition and laboratory tests. Five conditions might elevate the RI, and they are listed in table 2.

Parenchymal Complications

Parenchymal complications need to be ruled out initially, and they include acute tubular necrosis (ATN), rejection and cyclosporine toxicity.

Acute Tubular Necrosis

ATN, which is due to reversible ischemic damage to the renal tubular cells prior to engrafting, affects 20–60% of cadaveric renal grafts in the first 48 h. The sonograph-

Table 1. Causes of true renal graft rejection

	Immediate (<1 week)	Early (1–4 weeks)	Late (>1 month)
Vascular	renal vein thrombosis renal artery thrombosis	renal vein thrombosis	renal artery stenosis
Parenchymal	ATN hyperacute rejection accelerated acute rejection acute rejection	acute rejection	acute rejection chronic rejection cyclosporine toxicity infection recurrent ESRD
Urologic	ureteral edema/obstruction	urinary leak/fistula/urinoma	ureteral strictures
Collections	bleeding abscess	urinoma	lymphocele
Tumors			dermatologic cancers lymphomas PTLD
Iatrogenic	bleeding/hematoma arteriovenous fistulas pseudoaneurysms		

ESRD = End-stage renal disease; PTLD = posttransplant lymphoproliferative disorder.

ic appearance of ATN is variable; thus, the transplanted kidney might appear normal, but in severe cases it will look enlarged and edematous, with loss of corticomedullary differentiation. The renal sinus may appear compressed or obliterated due to swelling. Severe ATN will cause an elevation of the RI (>0.8), but a normal RI in conjunction with ATN can occur, especially in the first 24 h postoperatively [4].

Rejection

Rejection can be further divided into acute rejection, accelerated acute rejection and chronic rejection.

(a) Acute rejection occurs in 20–30% of cadaveric grafts, with the sonographic appearance revealing graft enlargement due to edema, decreased cortical echogenicity, swelling of the medullary pyramids resulting in loss of corticomedullary differentiation and edema within the renal sinus fat. When severe rejection occurs, pulsed Doppler might reveal a reduced, absent or reversed diastolic flow with elevation of the RI. A recent study published in 2011 showed that RI can lack sufficient sensitivity and specificity in patients with biopsy-proven rejection; indeed, over 50% of grafts have normal RIs <0.7 [5]. On the other hand, ATN and rejection might not be distinguished based on a single abnormal RI, since

Table 2. Causes of a high RI

Parenchymal	acute tubular necrosis rejection cyclosporine toxicity hypovolemia
Vascular	renal vein thrombosis ureteral obstruction/kinking
Anatomical/urological Technical considerations Pseudorejection	extrinsic graft compression

both entities may occur at the same time during the early postoperative course. Ultrasound-guided biopsy will be performed in this setting to differentiate between them.

(b) Accelerated acute rejection will occur basically within 1 week and may present with decreased urine output and rising creatinine levels. It results in poor graft success, reaching barely 40%. Ultrasound appearance is similar to acute rejection and ATN [6].

(c) Chronic rejection will present months to years after transplantation and will result in vascular issues and renal deterioration. Ultrasound will reveal a small graft with a tinned cortex, in addition to an RI that can be normal or slightly elevated.

Fig. 2. Case of a 59-year-old male with end-stage renal disease secondary to diabetes mellitus, HTN who underwent a living unrelated kidney transplantation at American University of Beirut Medical Center in February 2012. Combined analytical fluctuation of serum creatinine, glycemia and cyclosporine levels showed that serum creatinine level normalized after postoperative day 8 when tight glycemic control was maintained.

Table 3. Causes of pseudorejection

Hyperglycemia
Ureteral obstruction
Lymphocele
Arterial stenosis
Infection
Recurrence of primary pathology

Cyclosporine Toxicity

Cyclosporine toxicity is the reason behind kidney function deterioration when high levels of cyclosporine are reached, because it has a direct nephrotoxic effect on the kidney. It may occur at any time postoperatively, and unfortunately, ultrasound can show nonspecific findings and is frequently normal [7].

Pseudorejection

Pseudorejection is defined as an episode of significant elevation of serum creatinine (>25%) that is retrospectively found not to be caused by a true rejection. These incidents, when recognized, are treated accordingly without rejection therapy, sparing the patient all the side ef-

fects of intravenous pulse steroids and OKT3. Six causes of pseudorejection have been identified (table 3) and are discussed below.

Hyperglycemic Pseudorejection

Hyperglycemic pseudorejection was described for the first time in 1976 by Matas et al. [8] in the USA, at the University of Minnesota. In their case report, significantly elevated creatinine levels were found in association with hyperglycemia in diabetic transplant recipients. The creatinine levels returned to normal as soon as blood sugar was corrected. Well before this phenomenon was recognized, most of these surgical patients were readmitted and treated with antirejection therapy, exposing them to the numerous side effects. Therefore, since this phenomenon was identified, when the stable diabetic transplanted patient presents with a rising creatinine postoperatively in association with hyperglycemia, the blood sugar should be corrected first, with aggressive insulinotherapy, possibly requiring multiple regimens, while the serum creatinine level is monitored. Matas et al. [8] report the case of a 36-year-old diabetic female who underwent a living related kidney transplantation. Her postoperative creatinine was normal and remained in the normal range for a period of 3 months. She had type 1 diabetes mellitus that was well controlled on an outpatient basis during these 3 months, but after that period, creatinine started to rise progressively, with the glucose level reaching almost 800 mg/100 ml. A mean increase in blood glucose of 100 mg/100 ml was found to increase serum creatinine by 0.5 mg/100 ml. The patient was readmitted to the hospital, and as soon as sugar was tightly controlled, the serum creatinine level normalized even on the second day.

In conclusion, multiple factors can affect the serum creatinine level [9–11].

It seems that glucose cannot affect serum creatinine by a direct mechanism [8]. Instead, it is the hyperosmolarity caused by the hyperglycemia that will result in an elevation of serum creatinine levels. An increase in glycemia of 500 mg/100 ml will definitely increase the osmolarity by 27.8 mOsm/l, resulting in an increase in the extracellular osmolarity [12]. This will result in a shift of water outside the cells, resulting in a relative intracellular 'dehydration'. Since the renal threshold for glucose is exceeded, this 'glucose-induced' osmotic diuresis will result in a loss of fluids and electrolytes. This loss of fluids will result in a contracted plasma volume. At this level, the association of hyperosmolarity and relative intracellular and extracellular dehydration might deteriorate the kid-

ney function, resulting in the elevated serum creatinine level associated with hyperglycemia (fig. 2).

Ureteral Compression/Obstruction

Ureteral complications are one of the most frequent issues encountered after kidney transplantation, in 2–26% of reported series [13–33]. Ureteroneocystostomy is used routinely [13–17, 24, 25, 30], ureteroureterostomy [19, 20, 22, 34] and pyeloureterostomy [19] less frequently, and each technique has its pearls and pitfalls [29]. Most ureteral complications occur early in the postoperative course, and urinary fistula represents the most frequent one. In the late postoperative period, other concerns will be considered, including stenosis [23, 29, 30], cutaneous urinary fistulas [21, 23, 27, 28, 30], ureterolithiasis [26], periureteral abscess and fibrosis [18, 33]. Imaging modalities will help to rule out these complications, in addition to a high index of suspicion. Ureteral obstruction that can mimic an acute rejection has been reported, and a surgical reintervention will directly lower the serum creatinine level, sparing the patient a biopsy or unnecessary treatment with pulse steroids. A very important aspect would be to notice that serum creatinine would improve slightly, in the case of a ureteral compression, when steroids are started erroneously with an incorrect diagnosis of rejection, and one should not be induced into error in the face of this improvement. It is simply due to the fact that steroids will act as anti-inflammatory agents and will decrease the local inflammation around the site of obstruction, allowing a ‘transient’ passage of urine, thus transiently improving the serum creatinine level. However, the urologic surgeon should be able to distinguish these two entities and should have a very high index of suspicion.

Infection

Bacterial, viral or fungal infections may occur during the postoperative period in a transplanted patient. This is mainly due to the immunosuppressed status of the patient. Elevated serum creatinine levels are associated with bacterial infection and may be due to multiple factors. A febrile patient needs more fluids, and being dehydrated may contribute to this high creatinine level. Sometimes, an oral infection (tonsillitis) may be the cause, limiting any oral intake. However, in those cases, creatinine increases moderately, and this is not severe (<100%) [35, 36]. Viral infections [37–40], especially cytomegalovirus, have been associated with pseudorejection, including an increase in creatinine and some histological changes.

Lymphocele

Lymphocele is not infrequently found during the postoperative period in renal transplanted patients. It may occur in 1–18% of cases [41–44]. The reason is a lymphatic leak from the recipient lymphatic channels [41]. Rejection episodes result in an increase in lymphatic flow. Diuretics, ureteral obstruction [41] and high doses of steroids have also been shown to increase renal lymphatic flow and may exacerbate lymphocele formation. Once formed, a lymphocele might deteriorate kidney function by compressing the ureters, the bladder, the graft or even the vessels [41–44]. Lymphocele has been shown to be a cause of pseudorejection [41, 43, 44]. At the Mayo clinic, the most common presentation of patients with lymphoceles was elevated serum creatinine [45]. This was also clear in the series of Schweizer et al. [46].

Arterial Complications

A renal artery stenosis will result in an increase in serum creatinine level, as described by Simmons et al. [3] in 1977. Other cases were described shortly thereafter [47]. This can occur even in the nontransplanted patient [48]. Arterial stenosis induces an elevation in the serum creatinine level due to renal ischemia distal to the stenosis. Again, as in ureteral obstruction, in case the urologic surgeon thought that rejection had occurred and the patient is being treated with steroids and is improving with a slight decline in serum creatinine level, one should not be induced into error and attribute this to rejection and successful treatment thereof. It is in fact an arterial stenosis, and the patient responds transiently because steroids have a ‘mineralocorticoid-like’ effect that stimulates the renin-angiotensin-aldosterone system, thus causing absorption of sodium and fluid and transiently increasing the intravascular volume and consequently the blood flow to the graft, decreasing renal ischemia.

The incidence of posttransplant renal artery stenosis fluctuates between 5 and 12% [47] and should be promptly taken into consideration.

Recurrence of the Primary Pathology

Recurrence of the original disease after kidney transplantation is an issue, especially when caused by an immunologic mechanism or deposits of proteins and antibodies in the kidney [49–53]. Recurrent disease will appear in the chronic setting, rather than acute rejection [54, 55]. Recurrence of both focal glomerulosclerosis and membranoproliferative glomerulonephritis is more frequent in the pediatric population [56]. They may lead to

an increase in serum creatinine level as well and will present with proteinuria. The main concern is that these pathologies may be hidden in the presence of a concomitant rejection that is responding partially to antirejection therapy. Other primary diseases have also been found to recur, including dysplasia of the kidneys, polycystic kidney disease, diabetic nephropathy, amyloidosis and other metabolic diseases [57–59].

Discussion

Nowadays, kidney transplantation is the best treatment for patients with end-stage renal disease and is proved to increase survival. However, that does not mean that this surgical intervention always results in an uneventful postoperative course. During that period of time, multiple factors need to be monitored, including serum creatinine level. An elevation of the creatinine level may suggest a graft rejection, if the index of suspicion is high. Otherwise, we have to keep in mind that administration of antirejection therapy in the face of a low index of suspicion is not the standard of care. Furthermore, Zhang et al. [60] defined a condition called hyper-delayed graft function, where renal transplant recipients may experience delayed graft function, but recovery can take many months. ATN during or soon after surgery is the most common cause of hyper-delayed graft function, and after standard treatment, the vast majority of patients recover fully in 1–2 months.

Therefore, it is crucial to know that multiple other factors may affect renal function in the transplant recipient, and each one may result in an elevation in serum creatinine level, mimicking a rejection episode. One should not rush immediately to perform a biopsy of the transplanted kidney; on the other hand, one should remember that sometimes transplanted patients may refuse or delay biopsy.

Therefore, by gathering all the information provided and utilizing the clinician's armamentarium, including at least a blood glucose level, a Doppler ultrasound of the transplanted graft with its RI and a cyclosporine level, we will be able to identify the above factors that cause a pseudorejection with a significant elevation of serum creatinine (>25%) that is retrospectively found not to be caused by a true rejection.

These 6 factors should always be kept in mind: (1) hyperglycemia, (2) ureteral obstruction, (3) lymphocele, (4) arterial stenosis, (5) infection and (6) recurrence of primary pathology.

Hyperglycemia seems to be one of the most crucial factors, since diabetics represent a significant proportion of patients with end-stage renal disease undergoing kidney transplantation. The relative intracellular 'dehydration' caused by hyperglycemia underlies this event, and in general, a mean increase in blood glucose of 100 mg/100 ml will increase serum creatinine by 0.5 mg/100 ml.

Ureteral obstruction and lymphocele are frequent entities as well, occurring in up to 20% of cases; imaging modalities will easily rule them out. A careful dissection when harvesting the kidney from the donor should be kept in mind, and the periureteral tissue with its vascular supply should be preserved in order to avoid ureteral ischemia and a postoperative stricture. In parallel, lymphocele could be avoided by making sure to tie the surrounding lymphatics that have been exposed and cut, during grafting, in the recipient's iliac fossa.

An arterial stenosis of the transplanted kidney is less frequent and will be identified while performing an ultrasound of the graft.

In conclusion, it is of great importance to maintain tight glycemic control, especially in the diabetic transplanted patient who develops a pseudorejection with high creatinine, in order to avoid unnecessary antirejection therapy with its numerous side effects.

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