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Delayed Graft Function and Tacrolimus Overdosage: A Case Report

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Rezumat

Funcția întârziată a grefei și supradozajul cu Tacrolimus: prezentare de caz

Funcția întârziată a grefei (DGF) este o condiție frecvent asociată transplantului renal şi poate complica evoluția ulterioară a grefei renale. Există multipi factori implicați în dezvoltarea DGF, o parte dintre aceştia pot fi evitați printr-o gestionare atentă, în timp ce alții nu pot fi corectați. Sindromul Gordon sau pseudo-hipoaldosteronismul de tip II şi nefrotoxicitatea indusă de inhibitorii de calcineurină sunt complicații care pot precipita dezvoltarea DGF. Aceste manifestări nefavorabile pot apărea ca urmare a unui nivel crescut al tacrolinemiei secundar începerii tratamentului cu ICN şi pot fi prevenite prin monitorizarea atentă a concentației plasmatice a tacrolimusului. Am prezentat un caz al unei paciente în vârstă de 58 de ani care a fost admisă ca receptor pentru transplant renal cadaveric (KT) şi care a dezvoltat toate complicațiile asociate sindromului Gordon-like şi nefrotoxicității, inclusiv DGF. S-au constatat, în urma investigațiilor, niveluri crescute ale tacrolinemiei, generate de inițierea tratamentului cu ICN.

Cuvinte cheie: transplant renal, funcția întârziată a grefei, inhibitorii de calcineurină, sindromul Gordon-like

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Abstract

Delay graft function (DGF) is a condition that is frequently

associated with kidney transplantation and could complicate subsequent evolution of the renal graft. There are multiple factors implicated in the development of DGF, some avoidable through careful management, others without the possibility of correction. Gordon syndrome or type II pseudo-hypoaldosteronism and nephrotoxicity induced by calcineurin inhibitors are complications that can precipitate the development of DGF. These unfavorable manifestations can occur after high levels of Tacrolimus secondary starting calcineurin inhibitors treatment and can be prevented with careful monitorization of its levels. We reported a case of a 58-year-old patient who was admitted as receptor for cadaveric kidney transplantation (KT) and developed all the complications associated with Gordon-like syndrome and nephrotoxicity including DGF in the context of high Tacrolimus levels after starting calcineurin inhibitors treatment.

Keywords: kidney transplant, delayed graft function, calcineurine inhibitors, Gordon-like syndrome

Introduction

Delayed graft function (DGF) is a common complication in kidney transplantation KT), ranging between 20-40%. It is characterized by the need for dialysis within the first week after KT and is associated with increased morbidity, prolonged hospital stays, and potential long-term impacts on graft survival (1). Among the multiple causes of DGF, calcineurin inhibitors are commonly involved. Tacrolimus, a cornerstone in immunosuppressive therapy, is essential for preventing acute rejection. However, its narrow therapeutic index and potential for nephrotoxicity necessitate careful dose adjustments and monitoring. Overdosage can exacerbate graft dysfunction and compound the challenges associated with DGF. In addition, tacrolimus overdosage could produce other unfavorable effects such as confusion, drowsiness, hypertension, headache, nausea, tremors and electrolyte imbalances such as metabolic acidosis, hyperkalemia, hypomagnesemia, hypercalcemia, hyperuricemia (2). The mechanisms by which Tacrolimus overdose causes acute nephrotoxicity, which underlies DGF, are the following: vasoconstriction of afferent and efferent arterioles due to endothelial dysfunction, direct tubular injury, application of oxidative stress and favoring pathways involved in fibrosis (3-5). Moreover, Tacrolimus has been observed to increase the activity of the WNK-SPAK pathway, which governs the function of the sodium-chloride cotransporter (NCC) in the distal convoluted tubule. This upregulation can lead to enhanced sodium reabsorption and reduced potassium excretion, leading to hypertension, hyperkalemia and metabolic acidosis mimicking the effects of Gordon syndrome (6).

We point to discuss the clinical presentation, diagnostic challenges, and therapeutic interventions in a patient with delayed graft function and Gordon-like syndrome due to tacrolimus overdose.

Case Report

We present the case of a 58-year-old female patient with end stage renal disease due to type 2 diabetes mellitus (DM), who was admitted as receptor for cadaveric kidney transplantation (KT). She started dialysis five years ago, had good control of DM with normal body mass index (23.8 kg/m2) and no history of donor specific antibodies. The donor was a 45-year-old man, whose death was caused by an intracranial hemorrhage secondary to an aneurysm rupture. Donor-recipient HLA matching was 41.7% and cold ischemia time was 6h. Induction immunosuppressive therapy consisted of basiliximab, administered as 20mg in day 0 and day 4, and intravenous methylprednisolone (500 mg – day 0 and day 1, 250 mg – day 2, 125 mg – day 3).

Maintenance of immunosuppression was based on immediate-release tacrolimus, mycophenolate mofetil and oral prednisone. Tacrolimus was started with a dose of 0.2 mg/kg/day, adjusted to maintain a blood concentration of 10-15 ng/ml in the first 2 weeks post-transplantation.

Post-transplant evolution was slightly favorable until day 4, with serum creatinine decrease from 6.70 mg/dl to 4 mg/dl with a diuresis up to 2500 ml / 24 h (*Figs. 1, 2*). Tacrolimus trough level was at the upper therapeutic range. By day 4 serum creatinine started to increase in association with oliguria, hyperkalemia and metabolic acidosis onset. In addition, tacrolimus trough level increased to 30 ng/ml. In this context tacrolimus administration was stopped for 24h and resumed with a dose reduced by 50%. By day 7, creatinine increased to 9.87 mg/dl, with persistent oliguria, hyperkalemia metabolic acidosis, along with poor control of blood pressure and pulmonary congestion. Thus, a hemodialysis session was necessary. Doppler ultrasound and computed tomography of the abdomen did not reveal Doppler signal abnormalities of the graft vessels or obstructive pathology.

Until the overdose of Tacrolimus and the onset of DGF, the patient was receiving antihypertensive treatment with calcium channel blockers, beta-blocker and intravenous furosemide. Subsequently, in the context of poor BP control, persistent hyperkalemia and acidosis, rilmenidine and sodium bicarbonate were introduced in the treatment. Adjusting the dose of Tacrolimus to decrease the tacrolimus level in the target, as well as the previously mentioned measures, did not lead to an immediate decrease in serum creatinine and better control of BP and hyperkalemia, so that the patient required a session of HD. After the dialysis session, furosemide was replaced with a thiazide-like diuretic. The

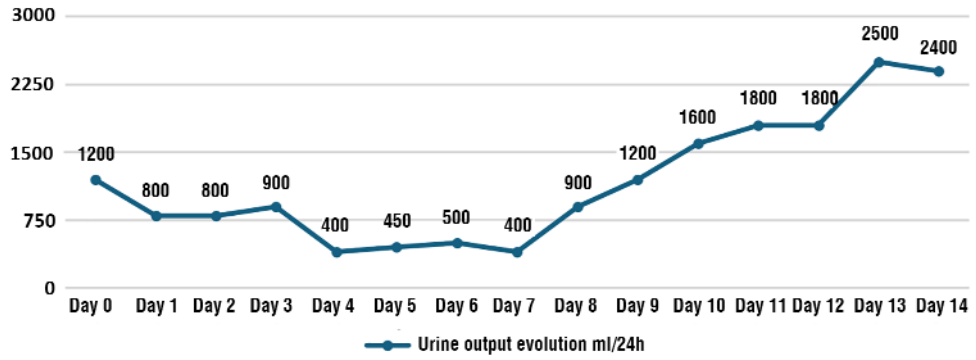

Figure 1. Urine output evolution per day

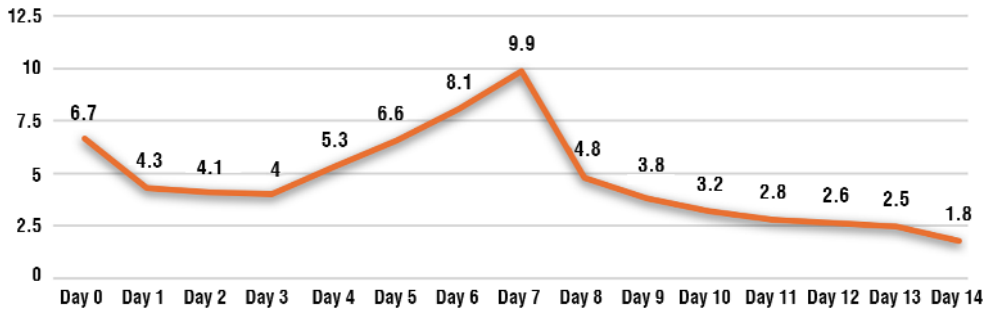

Figure 2. Creatinine level evolution

introduction of this diuretic, together with the final effect of Tacrolimus dose decrease, slightly augmented by the need for a dialysis session, led to a favorable evolution of renal function, correction of metabolic acidosis and hyperkalemia, and optimal BP control. The need for antihypertensive medication decreased significantly, the patient remained on thiazide-like diuretic only. On day 14 serum creatinine decreased to 1.78 mg/dl, blood pressure was normal under diuretic treatment, urinary output increased to ~ 2500ml/24h, and the electrolyte and acid-base parameters were within normal limits, so the patient was discharged (*Figs. 1-4*).

Discussion

Gordon syndrome or type 2 pseudo-hypoaldosteronism is defined by a mutation in WNK kinases that activate NCC and leads to impaired function of the sodium-chloride cotransporter in the distal convoluted tube. Affecting this cotransporter involves the development of hypertension, metabolic acidosis and hyperkalemia secondary to increase reabsorption of sodium and chlorine and decrease potassium secretion (7,8) (*Figs. 3, 4*). An important component of metabolic acidosis may be also an increased secretion of distal bicarbonate

Considering the constellation of clinical and biochemical signs identified in our patient, we can assume that we are dealing with Gordon-like syndrome induced by increased levels of Tacrolimus. This is also supported by improved renal function after decreasing tacrolimus levels and after adding a thiazide diuretic. In literature, the association between increased levels of tacrolimus

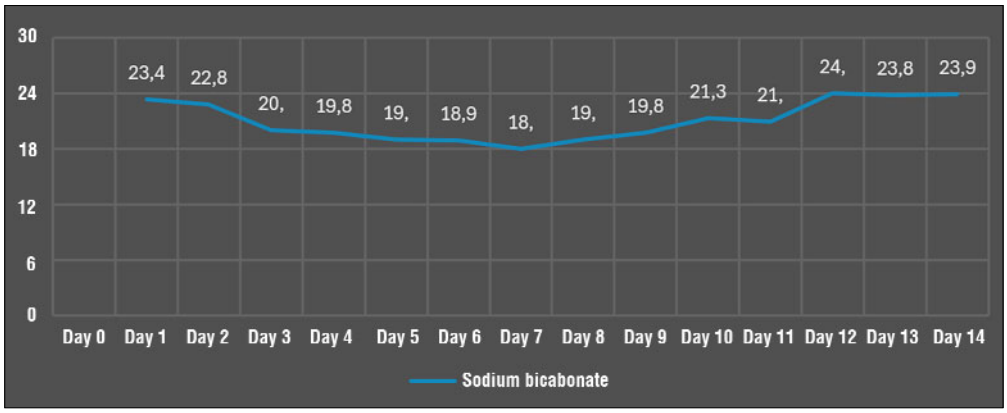

Figure 3. Serum sodium bicarbonate evolution

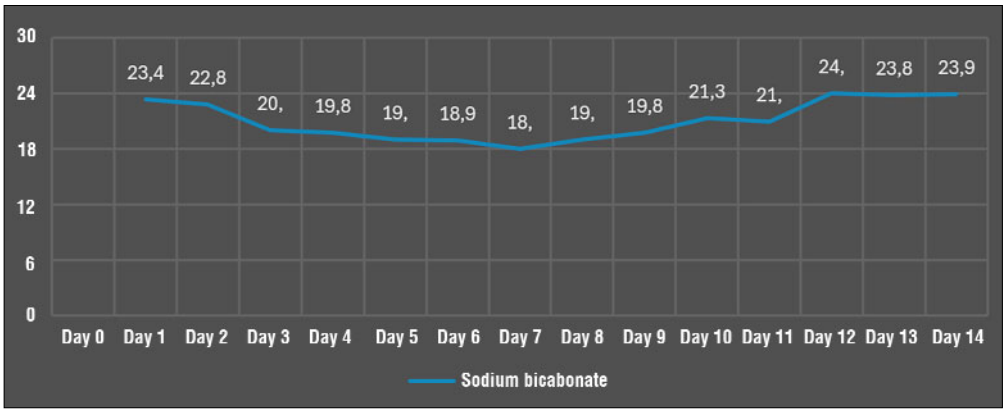

Figure 4. Serum potassium evolution

Table 1. Risk factors for DGF in kidney transplant recipients

Donor Related	Recipient Related	Perioperative
Deceased donor	Pretransplant dialysis Previous kidney transplant(s)	Hemodynamic instability Calcineurin inhibitors
Donation after cardiac death	HLA mismatch	Nephrotoxic antibiotics
Longer WIT >45 mim and/or CIT >24 H2	ABO incompatibility	Nephrotoxic analgesics
Gordon like syndrome		
Organ quality	Comorbidities	
Donor age >50 years	Higher body mass index	
Acute Kidney Injury	African American ethnicity	
Higher body mass index		
Shipping distance		
African American ethnicity		

and Gordon like syndrome is well proven, and there are numerous studies supporting this theory (8-10).

The occurrence of Gordon Like Syndrome together with nephrotoxicity caused by calcineurin inhibitors increases the risk of developing DGF (11).

DGF is frequent complication widely debated in medical literature whose main definition remains the need for dialysis in the first week post-transplant. The main risk factors that can lead to DGF are exemplified in *Table 1* (12). Apart from organ quality, all other criteria can be easily evaluated. Organ quality can involve the interpretation of a biopsy from the kidney graft and molecular investigations, these being risky and time-consuming investigations, so most of the time the opinion for the quality of the graft remains at the discretion of the clinician. The main risk factors for DGF in the case of our patient are deceased donor, pretransplant dialysis and calcineurin inhibitors

If we refer to the donor, he was a young patient, with no comorbidities associated with a perfectly functional renal graft - creatine at the time of harvesting 1.04 mg/dl. Regarding the optimal time to perform kidney transplantation: preemptive or after the initiation of dialysis, we have multiple articles written in the literature. Although preemptive transplantation is preferred, the subject remains open to research with many pros and co results.

In the case of our patient, the very high level of tacrolimus in the first days post-transplant, with all its intensively studied side effects: nephrotoxicity (up to the need for dialysis in Z7PT) acidosis, hyperkalemia, hypertension, nausea makes us say that the difficult evolution with the appearance of DGF is due to nephrotoxicity and Gordon like syndrome induced by calcineurin inhibitors. This is evident by the improvement of clinical and paraclinical parameters when tacrolimus approaches the desired level (*Figs. 1-4*).

Conclusion

In conclusion, tacrolimus overdose remains an important cause of DGF after KT and may lead to the development of Gordon-like syndrome. Strict monitoring of tacrolimus levels, dose reduction in case of overdosage, and the use of thiazide or thiazide-like diuretics are essential for the correction of DGF and Gordon-like syndrome.

Conflicts of Interests

The authors declare no conflict of interest.

Ethical Statement

The study protocol was approved by the Ethical Committee of Fundeni Clinical Institute (registration number: 21189).

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