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Delayed Graft function and Immunosuppressive Drugs in Kidney Transplantation: Cytokine Release Syndrome successfully treated with Adjuvant Hemoadsorption Therapy

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Abstract

Background: Pre-emptive kidney transplantation improves patient outcomes by avoiding dialysis-related complications; however, it carries a risk of delayed graft function (DGF) and acute rejection, particularly in high-risk recipients. Anti-thymocyte globulin (ATG), frequently used for immunosuppression, may induce cytokine release syndrome (CRS), a severe inflammatory condition associated with multi-organ dysfunction.

Case Presentation: We report the case of a 23-year-old male with IgA nephropathy who developed severe CRS with multi-organ involvement following recurrent ATG administration after kidney transplantation. The patient presented with acute kidney injury, acute respiratory distress syndrome (ARDS), and hemodynamic instability requiring vasopressors and intensive care support. Continuous renal replacement therapy (CRRT) was initiated, and a CytoSorb® hemoadsorption cartridge was integrated into the circuit to modulate the cytokine response. Three consecutive 24-hour hemoadsorption sessions resulted in rapid clinical improvement, including hemodynamic stabilization, restoration of renal function, and respiratory recovery.

Conclusion: This case illustrates the potential role of cytokine adsorption as an adjunctive strategy for managing severe CRS in the post-transplant setting. CytoSorb hemoadsorption contributed to the reversal of multi-organ dysfunction, supporting its application in the treatment of hyperinflammatory complications following immunosuppressive therapy. Further studies are warranted to validate its efficacy and define optimal clinical use.

Keywords: Cytokines release syndrome; Delay graft function; Cytosorb; Anti-thymocyte globulin; Continuous renal replacement therapy

Introduction

Pre-emptive kidney transplantation is associated with improved survival and quality of life, avoiding the need for dialysis and its complications [1,2]. However, the risk of delayed graft function (DGF) and acute rejection remains, particularly in high-risk donors and recipients [3-5]. Additionally, certain immunosuppressive drugs, such as anti-thymocyte globulin (ATG), can lead to severe adverse effects, including cytokine release syndrome (CRS) [6,7], which affects multiple organ systems [8-10]. The aim of this case report is to present a clinical case supporting the hypothesis that modulating cytokine

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levels through blood purification may represent a potential adjuvant strategy to mitigate CRS-induced injuries and multi-organ dysfunction [11-13].

Case Presentation

We present the case of a 23-year-old male patient (60 kg) with IgA nephropathy (Berger's disease) [14] who underwent pre-emptive kidney transplantation. Written informed consent was obtained from the patient for publication of this case report and any accompanying images in compliance with the Helsinki Declaration. In the immediate postoperative period, DGF occurred and was initially managed with tacrolimus, mycophenolic acid, and repeated ATG administration. ATG are polyclonal antibodies directed against human T-cell antigens, produced by immunizing animals (typically rabbits or horses). Twenty days post-transplant, the patient developed severe CRS after a recurrent ATG cycle, leading to multi-organ dysfunction. On ICU admission, the patient presented with acute kidney injury (serum creatinine: 3.49 mg/dl), lactic acidosis (lactate: 4.8 mmol/l), acute respiratory distress syndrome (ARDS), and cardiovascular instability (mean arterial pressure, MAP: 60 mmHg), requiring norepinephrine (0.26 µg/kg/min), dopamine (5.55 µg/kg/min), and levosimendan (0.05 µg/kg/min). From the first day of admission to the intensive care unit (ICU), mechanical ventilation was initiated due to worsening respiratory function (PaO_2/FiO_2 ratio: 42). CRRT was started for renal support at third day from ICU admission. The CRRT modality employed was continuous veno venous hemofiltration (CVVH), with a Polyarylethysulfone (PAES) membrane (Prismaflex HF 1400, Baxter); the technical specifications of the CRRT used are summarized in figure 1. A Cytosorb® hemoadsorption cartridge [15,16] was incorporated into the CVVH circuit to modulate the cytokine cascade involved in CRS and organ dysfunction. The Cytosorb filter consists of a cartridge filled with biocompatible, highly porous polymer beads made of polystyrene-divinylbenzene, capable of adsorbing hydrophobic molecules up to approximately 55 kDa. CytoSorb functions through non-selective adsorption, enabling the broad-range elimination of circulating cytokines [15,16]. Three consecutive 24-hour Cytosorb cycles were performed until clinical stabilization was achieved. Figure 2 illustrates the results related to the progression of mean arterial pressure (MAP) values and the dosage of vasoactive drugs in relation to the extracorporeal replacement therapies applied during the ICU stay. The combined treatment resulted in significant hemodynamic improvement, with MAP stabilization and gradual weaning off inotropic support. Renal function normalized, and diuresis resumed. By day 9, the patient was extubated. The Sequential Organ Failure Assessment (SOFA) [17] score improved from 17 at admission to 12 at the end of treatment and further decreased to 4 at ICU discharge on day 13, with the patient in stable condition (Table 1).

Discussion

This case report highlights the successful application of hemoadsorption therapy as an adjunct to conventional treatments for CRS associated with delayed graft function DGF and recurrent ATG administration in kidney transplantation. CRS is a critical and potentially life-threatening complication of immunosuppressive therapy, particularly with ATG, due to its ability to trigger an exaggerated release of pro-inflammatory cytokines that may lead to multi-organ dysfunction [3,6,7]. In detail, ATG binds multiple T cell surface antigens (e.g., CD2, CD3, CD45, HLA-DR), triggering receptor cross-linking and subsequent activation of T cells and monocytes. This activation leads to rapid secretion of pro-inflammatory cytokines, including IL-2, IL-6, IFN-γ, TNF-α, and IL-1β, initiating an autocrine/paracrine amplification loop.

CRRT setting	**CVVH**: provides convective clearance by filtering a large volume of blood. Replacement fluid restores volume lost.
Blood flow rate (Qb)	120 ml/min
Target Tri-sodium CITRATE	2.7-3 mmol/l
Post Filter Replacement fluid (Qr)	500 ml/h
Net fluid removal rate (Q_{net})	100 ml/h
Effluent dose	30.2 ml/kg/h
CVVH Filter	Prismaflex HF 1400

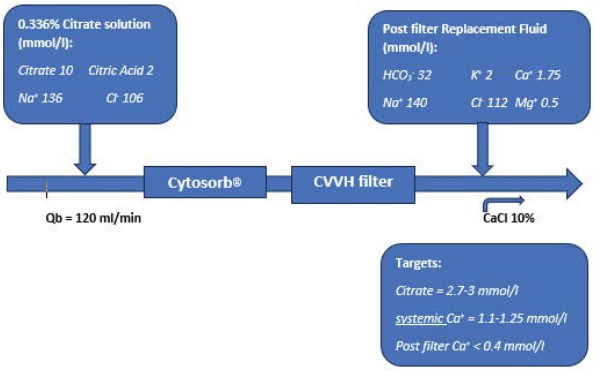

Figure 1: Setting of the CRRT dialysis circuit using regional citrate anticoagulation with the Prismax machine (Baxter). The Q_b was 120 ml/min. Citrate solution was added at the arterial catheter port and ionized calcium levels were sampled postfilter. Citrate flow rates were subsequently adjusted based on postfilter ionized calcium values to be maintained within a range of less than 0.4 mmol/L. The technique for fluid balance used a fixed ultrafiltration rate to achieve a target effluent dose of 30.2 ml/kh/h; Q_r was adjusted to 500 ml/h. Q_b, blood flow rate; Q_r, replacement fluid rate; CRRT continuous renal replacement therapy; CVVH continuous veno-venous hemofiltration.

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Table 1: Progression of clinical and laboratory parameters and patient scores during ICU stay. SOFA Sequential Organ Failure Assessment. MAP mean arterial pressure. WBC white blood cells. PCT Procalcitonine.

	ICU Admission	Day 3 – Start Cytosorb	Day 4	Day 5-	Day 6- Stop Cytosorb	Day 7	Day 8	Day 9
SOFA score	11	17	15	15	15	12	11	9
WBC (x10³/ml)	2.99	17.34	9.56	9.65	7.95	5.75	3.69	3
PCT (ng/ml)	19.89	>100	>100	>100	87.3	69.7	50.18	18.12
Lactate (mmol/l)	37.8	10.4	11.1	12.4	11.1	6.5	3.4	2
Creatinine (mg/dl)	3.49	5.28	2.5	1.39	1.07	1.13	1.06	1.05
MAP (mmHg)	60	63	117	87	112	91	90	95
Norephinephrine (µg/kg/min)	0.26	0.2	0.13	0.06	0.06	0.03	0	0
P/F	**181**	**42**	**289**	**396**	**467**	**494**	**722**	**-**

The cytokine surge stimulates innate immune cells (e.g., macrophages, neutrophils), which further propagate the inflammatory response through additional cytokine and chemokine release [7,11,8]. The patient in this case exhibited severe CRS characterized by cardiovascular instability, AKI, and ARDS, necessitating immediate intensive care interventions. The integration of a Cytosorb® hemoadsorption cartridge into the continuous veno-venous hemofiltration (CVVH) circuit provided a pivotal therapeutic approach. Hemoadsorption has been shown to effectively reduce circulating cytokine levels, mitigating the hyperinflammatory response characteristic of CRS [11-13,19]. The rapid hemodynamic stabilization observed in this case, including mean arterial pressure recovery and the successful weaning of vasoactive medications, underscores the potential of Cytosorb to modulate the cytokine cascade and support end-organ function [13,15,16]. Importantly, the normalization of renal function and respiratory parameters further emphasizes the role of cytokine modulation in addressing multi-organ involvement in CRS. These outcomes align with emerging evidence suggesting that hemoadsorption therapy can reduce the severity of organ dysfunction and improve clinical trajectories in critically ill patients with hyperinflammatory syndromes, such as sepsis and transplant-associated complications [11-14].

This case also highlights the necessity for a multidisciplinary approach in managing complex post-transplant scenarios. The combination of precise hemodynamic monitoring, tailored immunosuppressive regimens, and innovative extracorporeal therapies enabled comprehensive care for a patient at significant risk of graft failure and mortality. Despite these promising results, some limitations warrant discussion. The use of hemoadsorption therapy in CRS is still evolving, with a need for randomized controlled trials to validate its efficacy and safety in broader patient populations [15,19,20]. Additionally, the absence of direct measurements of cytokine levels in this case precludes definitive conclusions about the correlation between cytokine reduction and clinical outcomes.

This case illustrates the potential of hemoadsorption therapy as an adjuvant strategy to mitigate CRS-induced multi-organ dysfunction in the context of kidney transplantation. By effectively stabilizing hemodynamics, improving organ function, and potentially reducing the risk of graft rejection, hemoadsorption represents a promising intervention in the management of severe immunosuppressive therapy-related complications. Future research should aim to clarify the role of hemoadsorption in transplant medicine, with a particular focus on optimizing its application in high-risk patients.

Statements

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by local ethic committee CEAVNO, University of Pisa, Italy, approval number 25088.

Consent to publish statement: Written informed consent was obtained from the partecipant for publication of this case report and any accompanying images in compliance with the Helsinki Declaration.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Author contributions

Jacopo Belfiore, Maria Bindi, Ugo Boggi, and Giandomenico Biancofiore contributed to the drafting and thorough revision of the manuscript. Jacopo Belfiore also created figure 1 and table 1.

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Data availability statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author or from the Head of Transplant ICU upon reasonable request. All data are stored by the Transplant Intensive Care Unit of the University of Pisa, in compliance with current privacy regulations.

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