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Cytokine Removal under Hemodiafiltration with Endogenous Reinfusion in Acute Kidney Injury Secondary to Angioimmunoblastic T-Cell Lymphoma: A Case Report

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Key Words
Acute kidney injury · Cancer · Cytokines · Dialysis · Hypoalbuminemia

Abstract
Angioimmunoblastic T-cell lymphoma shows a high release of cytokines. Different blood purification techniques are employed to control hypercytokinemia. Here we investigated the effects of intermittent supra-hemodiafiltration with endogenous reinfusion on cytokine removal in a patient presenting with acute kidney injury. After the first day of chemotherapy for angioimmunoblastic T-cell lymphoma, a 78-year-old male patient developed acute kidney injury and systemic inflammatory response syndrome due to massive release of inflammatory cytokines. Three sessions of supra-hemodiafiltration were performed. Blood samples for evaluation of renal function and inflammatory mediators were collected at the beginning and the end of each dialytic session. A marked improvement of clinical state and renal function was associated to a significant reduction of inflammatory markers. Our results suggest that renal replacement therapy with supra-hemodiafiltration may remove a wide spectrum of inflammatory mediators and uremic toxins involved in acute kidney injury and systemic inflammatory response syndrome.

Introduction

Lymphoproliferative disorders often involve the kidney either by release of inflammatory mediators (i.e. pro-inflammatory cytokines and growth factors produced by bulky malignant lymphomas) or by deposition of paraproteins (i.e. κ or λ free immunoglobulin light chains in monoclonal gammopathies). Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) was first described in 1974 by Frizzera et al. [1] as a new disease entity. Recently, AILD was recognized as a mature T-cell neoplasm and termed angioimmunoblastic T-cell lymphoma (AITL) by the World Health Organization classification [2], although the abbreviation AILD is still used. AITL shows a high proportion of TNF-α-positive T lymphocytes and in addition the percentages of interleukin (IL)-2, IL-4, IL-5, IL-6, IL-13 and IFN-γ-positive T lymphocytes are relatively higher than in other lymphoproliferative diseases. This typical multiple hypercytokinemia suggests that in AITL the source of cytokines is within the lymph nodes. Modulation of the cytokine network may be one of the logical objectives of future therapeutic strategies designed for AILD [3]. Improved dialysis techniques as supra-hemodiafiltration with endogenous reinfusion (supra-HFR) are able to remove several medium-high molecular weight solutes (i.e. free immunoglob-

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Table 1. Main clinical features and laboratory findings during supra-HFR treatment

Variable	Baseline	1st HFR pre	1st HFR post	2nd HFR pre	2nd HFR post	3rd HFR pre	3rd HFR post
BUN, mg/dl	40	94	56	78	57	73	50
Creatinine, mg/dl	1.3	2.6	2.1	2.1	1.5	1.6	1.2
Total protein, g/dl	6.9	5.2	6.1	5.0	5.9	5.9	5.9
Albumin, g/dl	3.1	2.5	2.9	2.3	2.8	3.0	3.2
Hematocrit, %	35.3	28.6		28.4		30.2	
Sodium, mEq/l	138	129	134	135	136	136	135
Potassium, mEq/l	3.9	4.3	4.3	4.7	4.3	4.0	3.8
Calcium, mg/dl	9.0	7.3	8.1	7.8	8.9	8.7	9.5
Phosphorus, mg/dl	4.5	4.1	3.9	4.7	3.8	4.7	3.0
LDH, IU/l	525	235	190	206	172	174	187
IL-6, pg/ml	–	101	53.5	41	15.5	1	1
TNF-α, pg/ml	–	154	114.1	90	60.5	33.8	20.4
Body temperature, °C	39	40	37	37	36.5	36.5	36.5
Blood pressure, mm Hg	130/90	90/60	100/50	130/60	125/80	150/60	140/60
Heart rate, bpm	88	110	100	80	85	70	68
SpO_2 (FiO_2 21%)	98	93	96	96	97	98	99
Diuresis, ml	1,500	300		1,000		2,500	
Ultrafiltration, ml	–	2,200		600		300	

ulin light chains and pro-inflammatory cytokines together with other uremic toxins) with negligible loss of albumin and other nutrients [4]. We report the first case of a patient with AITL and systemic inflammatory response syndrome (SIRS) with acute kidney injury (AKI) treated with supra-HFR. Our main working hypothesis was the assumption that supra-HFR may remove by adsorption significant amounts of inflammatory mediators that may play a role as uremic toxins in SIRS-related AKI as well as in end-stage renal disease with negligible loss of essential nutrients.

Case Report

A 78-year-old male patient was admitted to our emergency department in March 2011 with fever, night sweats, loss of appetite, cough, fatigue, axillary and inguinal adenopathies. Clinical history reported non-insulin-dependent type 2 diabetes mellitus, chronic obstructive pulmonary disease, high blood pressure treated with ACE-inhibiting medications, cervical-urethral obstruction due to benign prostatic hyperplasia, and rheumatoid arthritis. In particular, no history of cardiovascular or renal disease, normal kidney function and no pathologic proteinuria were reported. On admission, the patient was conscious and hemodynamically stable, with a systemic blood pressure of 130/90 mm Hg and a heart rate of 88 bpm; blood gas analysis showed 98% O_2 saturation at room air and a body temperature of 39°C. The main baseline laboratory findings are reported in table 1. Renal function tests showed a BUN of 40 mg/dl, serum creatinine of 1.3 mg/dl. Estimated GFR calculated with the CKD-EPI formula was 53 ml/min; daily urine output was about 1,500 ml, and urinanalysis was negative. Renal ultrasound was normal. Thoracoabdominal computed tomography scan showed multiple supra- and subdiaphragmatic adenopathies. Biopsy of a pathological inguinal node demonstrated atypical lymphocytes. Clinical and pathological findings were consistent with AITL.

The patient was thus admitted to our department of hematology and started specific therapy with high-dose dexamethasone (20 mg daily) and doxorubicin (10 mg/m^2 on days 1, 3, 6, and 11).

After 1 day of cytotoxic therapy the patient showed progressive contraction of diuresis, fluid overload with azotemia and increased serum inflammatory markers (IL-6 and TNF-α), that was consistent with a SIRS with AKI. Intermittent renal replacement therapy was thus scheduled. Supra-HFR was preferred among other available treatment options for the possible removal of higher amounts of pro-inflammatory cytokines and other uremic toxins with negligible loss of albumin and other nutrients.

At the time of the first hemodialysis session, the patient presented with fever, hypotension, agitation that was treated with morphine (10–30 mg daily), petechiae in the lower limbs, dyspnea, generalized edema, dysproteinemia that was treated with 20% albumin 200 ml daily, oligoanuria resistant to fluid replacement and infusion of diuretics (furosemide 1 g daily), hyponatremia that was treated with infusion of Na chloride 80 mEq daily, anemia and initial loss of renal function (table 1).

We submitted our patient to three dialysis sessions of 3 h each on alternate days with the supra-HFR equipment (Bellco Srl, Mirandola, Italy) [4, 5]. A dual-lumen indwelling catheter was positioned in the right femoral vein as vascular access.

A two-chamber filter (Supra 17 – high permeability polyphenylene super high-flux 0.7 m^2 + polyphenylene low-flux 1.7 m^2; Bellco Srl) was used. Dialysate composition was 3 mmol/l K^+ and 1.5 mmol/l Ca^{2+}. A total conductivity of 13.8 ms/cm and 26 mmol/l HCO_3^- were maintained on average during the three ses-

more strongly than either convection or diffusion to cytokine removal in some membranes and that protein adsorption properties may represent key features of membrane material [7, 8].

HFR and Supra-HFR

HFR is a form of intermittent hemodiafiltration that utilizes separated convection, diffusion and adsorption [4, 5]. In supra-HFR a double-chamber hemodialyzer consisting of a 0.7-m^2 polyphenylene super high-flux convective dialyzer and a 1.7-m^2 polyphenylene low-flux diffusive dialyzer (Supra 17; Bellco Srl) is applied to obtain a complete physical separation between convection and diffusion. The two chambers of the filters are arranged in series. Pure ultrafiltrate (plasmatic water) obtained by the convective phase of the first stage passes through a adsorbent cartridge. The regenerated ultrafiltrate is reinfused into the bloodstream before the diffusive section of the filter. Convective and adsorptive stages do not involve any fluid subtraction as reinfusion to the diffusive dialyzer equals ultrafiltration. The adsorbent cartridge (Supra Sorb; Bellco Srl) is constituted by a cylindrical polycarbonate shaft containing spherical particles of undissolvable macroporous-structured hydrophobic styrene resin (50 ml) of about 150 μm diameter fixed by an internal treatment filter with about 1.5 μm of outlet filter (approximate surface area of 700 m^2 for each gram of resin). Free internal volume is filled with physiological solution. Unlike hemoperfusion, where the adsorptive cartridge is perfused by whole blood, in this case the cartridge is perfused by low-flux ultrafiltrate, with the advantage that the Q_{uf} is sharply less than the Q_b, with a subsequent longer contact between the ultrafiltrate and the resin within the cartridge and finally a higher adsorption of uremic toxins. This process, moreover, is devoid of problems related to coagulation and hemocompatibility, due to the absence of red blood cells, inflammatory cells and platelets in the ultrafiltrate. Treatment is performed with the Formula Plus monitor (Bellco Srl), equipped with a particular software program that automatically determines the best ultrafiltrate flow rate (Q_{uf}). The adsorbent cartridge has high affinity for several uremic toxins and middle molecules (β_2-microglobulin, homocysteine, λ and κ free light chains and chemokines and cytokines) [9]. Indeed, supra-HFR exploits the principle of selective adsorption that allows a targeted selection among the numerous substances of the ultrafiltrate due to the properties of the adsorbent resin within the Suprasorb cartridge. Urea, creatinine, uric acid, sodium, potassium, calcium, phosphate and bicarbonate are not adsorbed and remain unchanged after the passage through the cartridge. Thus the 'regenerated' ultrafiltrate is an endogenous ultrapure replacement fluid with a physiologic content of bicarbonate, amino acids and water-soluble vitamins. Blood mixed with such 'endogenous' reinfusion solution is managed in the second chamber of the filter during the second stage of hemodiafiltration, where the requested loss of fluid, electrolytes and small uremic toxins is obtained by diffusion. The efficiency of the adsorbent resin of the Suprasorb cartridge was investigated in vitro and in vivo by adsorption tests on middle- and high-weight molecules as IL-6 (24.5 kDa), factor D of complement and α_1-glycoprotein (43.5 kDa). In particular, the Suprasorb cartridge showed higher adsorption of middle- and high-weight molecules and negligible adsorption of albumin and other nutrients compared to conventional styrenic resin. Indeed, albumin and other nutrients are completely reinfused and not diffused in the second chamber of the filter. Such selectivity of the adsorption allows the increase of permeability of the convective section of the dialyzer. Hence, supra-HFR employs 'super high-flux' polyphenylene membranes that are characterized by a higher cut-off (42–45 kDa) compared to the 'high-flux' polyphenylene membranes (cut-off 35 kDa) of conventional HFR, as shown by the higher sieving coefficient reported for all molecular weights [9].

Recent positive results in the use of real-time monitoring systems to assess the cytokine network activation may further improve the precision and efficacy of blood purification techniques in the treatment of hypercytokinemia. Additional research for 'real-time' cost-effective determination of multiple cytokines in a single sample by a proteomic approach are necessary. Among others, the Evidence Investigator biochip system (Randox) method allows the simultaneous determination of cytokines, cytokine receptors and growth factors, over five multianalyte arrays. The combination of highly specific antibodies and advanced chemistries enables multiple cytokines and growth factors to be detected simultaneously in a single sample [10].

Our preliminary results, which need confirmation by further controlled clinical trials, confirm experimental data [4, 5–9] and suggest that supra-HFR is able to remove cytokines in vivo. Furthermore, the significant loss of albumin reported with high-flux dialysis and plasma exchange procedures is negligible with supra-HFR that is a clear advantage in critically dysproteinemic and malnourished elderly patients. Indeed patients with AITL may show hyponatremia and hypoalbuminemia at clini-

sions. Blood flow (Q_b) was 250 ml/min and dialysate flow (Q_d) was 500 ml/min. The ultrafiltrate flow rate (Q_{uf}) from the convective sector and the reinfusion were kept at 50 ml/min (endogenous total infusion volume about 900 ± 300 ml for treatment). The regenerated ultrafiltrate was obtained by an adsorbent cartridge containing 50 ml of hydrophobic styrene resin with a surface of 700 m^2 for each gram for resin (Suprasorb; Bellco Srl). Weight loss was 730, 200 and 100 g/h during the first, second and third dialysis sessions, respectively. About 1,000 ml of fresh frozen plasma was administered during the first and second dialysis sessions. Enoxaparin 2,000 IU was administered to maintain the circuit. Blood samples were collected at every dialysis session for evaluation of renal function and inflammatory markers IL-6 and TNF-α, 10 min before connection and 15 min after restitution. Quantitative assessment of IL-6 and TNF-α in human serum was carried out with ELISA kits (DRG ELISA).

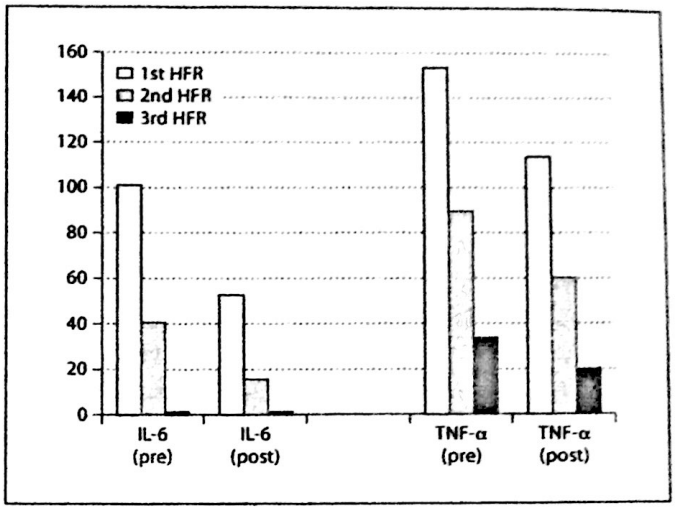

Fig. 1. Effect of the three sessions of supra-HFR on inflammatory markers. IL-6 decreased from 101 to 1 pg/ml and TNF-α from 154 to 20.4 pg/ml, respectively.

Results

Clinical features and laboratory findings during the supra-HFR treatment are reported in table 1. Weight loss was 730, 200 and 100 g/h during the first, second and third dialysis sessions, respectively. After the second supra-HFR session, urinary output increased up to 1,000 ml/24 h with a BUN of 57 mg/dl and a serum creatinine of 1.5 mg/dl. Furthermore, a reduction of body temperature up to 37°C and an improvement of sensory-cognitive functions were observed. Serum Na^+ rose up to 134 mEq/l and we decreased sodium daily infusion to 40 mEq. A further increase of urine output up to 2.5 l/day with subsequent reduction of furosemide infusion to 750 mg/24 h and a clear-cut improvement of renal function were observed after the third dialysis session. Moreover, the administration of albumin was also stopped after the third dialysis session for the increase of serum proteins and albumin. Clinical conditions (edematous state, petechiae in the legs, fever and agitation) also improved after the treatment. Finally, a good hemodynamic compensation with a systemic blood pressure of 140/60 mm Hg was achieved. Diuresis and renal function were normal at 2 months of follow-up. Supra-HFR led to a dramatic improvement of inflammation markers. Plasma IL-6 and TNF-α were significantly reduced during the three supra-HFR sessions and during the whole dialytic cycle as well (fig. 1).

Discussion

Humoral mediators including cytokines play key roles in the pathophysiology of critically ill patients. In particular, SIRS that may be observed in sepsis and occasionally during the course of hematological malignancies is a condition typically induced by excessive cytokine production. AITL shows a high proportion of TNF-α-positive T lymphocytes and in addition the percentages of IL-2, IL-4, IL-5, IL-6, IL-13 and IFN-γ positive T lymphocytes are relatively higher than in other lymphoproliferative diseases. Hence, AITL shows a high release of cytokines from the bulky tumoral mass or due to tumoral lysis during chemotherapy. This state of multiple hypercytokinemia may play a role comparable to sepsis in the pathophysiology of critical complications and may result in progression to SIRS and eventually to multiple organ failure in affected patients [1]. Proposed mechanisms of cytokine removal by blood purification techniques include convection, diffusion and adsorption. Among the various types of blood purification techniques currently available, continuous venovenous renal replacement therapies (CRRT/CVV–) including hemodialysis (CVVHD), hemofiltration/high-volume hemofiltration (CVVH/HVCVVH) and hemodiafiltration (CVVHDF) have been most extensively investigated for their effectiveness in cytokine removal. Investigations involving hemofilters/hemodialyzers for blood purification made of various materials, such as polysulfone, polyacrylonitrile (AN69), polymethylmethacrylate, ethylene vinyl alcohol, polyamide, and cellulose triacetate, have frequently revealed that the ability to remove cytokines varied depending on the membrane material employed [6, 7]. This difference led to the idea that adsorption contributes

cal presentation [11]. Supra-HFR thus may represent a highly biocompatible technique that is able to reduce serum inflammatory cytokines that may often worsen AKI. Unlike other treatment modalities as plasma exchange, supra-HFR makes possible and safe the use of high cut-off membranes without significant loss of albumin, in order to run a more physiological and selective treatment.

In conclusion, our preliminary experience, which needs confirmation in long-term studies, suggests that supra-HFR beyond it could help to reduce free immunoglobulin light chains [5], may obtain safe and effective cytokine removal and could be considered in the treatment of hypercytokinemia-associated AKI that may be triggered by cancer therapy, especially in hematological malignancies.

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Erratum

In the study by Claure-Del Granado and Bouchard: Acid-Base and Electrolyte Abnormalities during Renal Support for Acute Kidney Injury: Recognition and Management [Blood Purif 2012;34:186–193], the name of the first author was not complete. The correct last name is Claure-Del Granado.