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SHORT COMMUNICATION

Septic shock secondary to β-hemolytic streptococcus-induced necrotizing fasciitis treated with a novel cytokine adsorption therapy

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Introduction: *Numerous animal studies and preliminary data from a clinical trial in septic patients demonstrated that a decrease in blood cytokine levels using an extracorporeal cytokine filter (CytoSorb™) can effectively attenuate the inflammatory response during sepsis and possibly improve outcomes.*
Methods: *A 60-year-old female was admitted to hospital due to a forearm fracture. After surgical wound care by osteosynthesis the patient developed surgical wound infection which progressed to necrotizing fasciitis. All diagnostic criteria for SIRS were evident with additional proven infection from β-hemolytic streptococcus. On admission to the ICU, the patient presented a full picture of multiple organ dysfunction syndrome due to septic shock including kidney failure, lung failure as well as thrombocytopenia, metabolic acidosis, and arterial hypotension.*
Results: *After one day on mechanical ventilation and an IL-6 level of 70 000 pg/ml the patient was treated with CytoSorb therapy over a period of four days, resulting in a significant reduction of IL-6 to 66 pg/ml and an overall improvement of the patient's condition. Despite the necessity of enucleation, the patient was successfully stabilized until control of the surgical infectious source was achieved. Importantly, treatment was safe and well-tolerated, without any adverse events.*
Conclusions: *This is the first report of the clinical application of CytoSorb hemoadsorption in combination with a CRRT in a patient with septic shock. CytoSorb as described was able to significantly reduce IL-6 plasma levels and decrease vasopressor need while no adverse and device-related events occurred. CytoSorb seems to be an interesting and safe extracorporeal therapy to stabilize and bridge septic patients to surgery or recovery.*

Keywords: *Sepsis, Septic shock, Necrotizing fasciitis, Cytokine adsorption, Multiorgan failure*

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BACKGROUND

Extracorporeal blood purification techniques have gained increasing attention as possible adjunctive treatment for sepsis and other inflammatory states characterized by an overwhelming cytokine production. Thus far, several human pilot trials have tried to use non-optimized hemopurification techniques (originally developed for dialysis and end-stage renal disease) to achieve cytokine reduction (1). Of these, only high volume hemofiltration has shown slight benefit in treating certain aspects of sepsis (2, 3). A main shortcoming of most blood purification techniques is, however, their limited capacity to remove cytokines from the blood compartment resulting in the inability to significantly lower cytokine levels (4-6). Additionally, the need for large volumes of replacement fluid has rendered these techniques

impractical. Hemoadsorption using a novel polymer (CytoSorb, CytoSorbents Europe, Berlin, Germany) – applied as an extracorporeal cytokine filter cartridge – represents a promising alternative as adjunctive treatment of subjects with systemic inflammatory response in the setting of severe sepsis or septic shock. The CytoSorb polymer is both highly adsorptive and biocompatible, facilitating a concentration-dependent but size-selective removal of molecules with middle molecular weight (approx. 10-50 kDa). In this paper we report on a case of septic shock secondary to β-hemolytic streptococcus-induced necrotizing fasciitis successfully treated with CytoSorb therapy. Approval of the IRB was not required for this study, informed consent was obtained from the patient.

CASE PRESENTATION

A 60-year-old female with no pre-existing diseases except hypertension and hypothyroidism presented at the hospital with radius fracture of the right forearm after an accident. Immediate wound care was achieved by application of a plaster splint followed by operative osteosynthesis on the same day. A marked swelling of the forearm with a bleeding surgical wound was noticed two days post-operative. The following day, swelling dramatically worsened and expanded to the upper arm. At that time, no pulse was palpable. Of note, the patient experienced an oropharyngeal streptococcus infection 2 weeks before the incident. The patient collapsed and was transferred to the ICU where the following vital parameters were recorded: body temperature 35.9°C, heart rate 120 bpm, respiratory rate 30, systolic pressure 70 mmHg, the latter indicative for septic shock (APACHE II score of 19 and a SOFA of 8).

Antibiotic treatment (ampicillin, fosfomycin), vasopressor and volume therapy (goal-directed therapy) were initiated immediately. After operative fasciotomy on the same day, oliguric acute renal failure (cumulative urine output 300 ml/24 h) and acute respiratory distress syndrome developed, making the initiation of continuous veno-venous hemofiltration and mechanical ventilation necessary. Infection with β-hemolytic streptococci was proven later in the course of the day. Due to the rapid onset of the inflammatory response as assessed by an IL-6 of 70 000 pg/ml and the need for renal replacement therapy the decision to use CytoSorb™ as an adjunctive treatment was made. Of note, the time from initial blood withdrawal, measurement of IL-6, information of the physician about the IL-6 level of 70 000 pg/ml, setup and initiation of the CytoSorb procedure was approximately 3 h.

In total, three sessions of treatment with CytoSorb™ (CytoSorb cartridge, CytoSorbents, Monmouth Junction, NJ, USA) were performed over a period of four days with one treatment session per day using one cartridge for each treatment. Sessions were performed on the first day as well as on day 3 and 4 after ICU admission as follows: first treatment – 36 h, second treatment – 18 h, third treatment – 17 h. As the initial treatment was started late evening, we decided at the next days' shift change to run the procedure for another day, resulting in a total treatment time of 36 hours, notably without any adverse or device related events. Treatments two and three were then run in a normal interval of 17 h to 18 h. The CytoSorb treatment was performed in combination with standard continuous hemodialysis (CVVHD) (dialysate flow 2000-2150 ml/h, Fresenius Multifiltrate, Fresenius Medical Care, Bad Homburg, Germany) using regional citrate anticoagulation only of the external blood circuit and blood flow rates of 100 ml/min. Of note, the CytoSorb cartridge was placed before the hemofilter for CVVHD.

Markers of inflammation, organ dysfunction and need for vasopressors in the course of the three treatment sessions are outlined in Table I. After the first session, IL-6 plasma concentration decreased from 70 000 to 39 100 pg/ml (-44.3%). The final IL-6 level after the third session was 66 pg/ml (Fig. 1). Interestingly, IL-6 levels assessed directly after the CytoSorb cartridge were remarkably lower compared to those measured before the device, generally confirming clearance effectiveness of the cartridge (Fig. 2). Moreover, these removal rates were seen in a concentration-dependent fashion, pointing to the inherent autoregulatory property of the polymer (i.e., high cytokine concentrations – high removal rates, low cytokine concentrations – low removal rates).

Significantly, despite a considerable reduction in IL-6 levels, enucleation followed by vacuum-assisted closure therapy of both the lower and upper arm between the second and third treatment were inevitable. After the third CytoSorb treatment, hemofiltration was continued without CytoSorb as the need for vasopressors was significantly decreased and IL-6 levels were back in a normal range. CytoSorb in combination with CVVHD and regional citrate anticoagulation could be run continuously for up to 36 h without any adverse or device-related events during or after treatment.

TABLE I - MARKERS OF INFLAMMATION, ORGAN DYSFUNCTION, AND NEED FOR VASOPRESSORS

	Before first CytoSorb treatment	After first CytoSorb treatment	After last CytoSorb treatment	At discharge from ICU
Leucocytes (×10³ µl)	1850	13810	29000	6760
Platelets (×10³ µl)	194000	74000	49000	244000
IL-6 (pg/ml)	70000	39100	66	14.5
Cumulative urine output (ml/day)	200	410	410	2500
Creatinine (mg/dl)	2.07	1.88	1.37	0.79
Need for Noradrenalin (ug/kg/min)	1.18	0.24	0.08	0

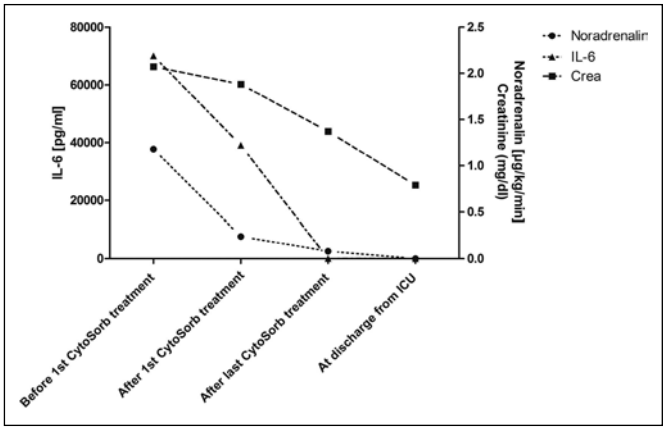

Fig. 1 - *Plasma concentrations of IL-6 and creatinine and the need of noradrenalin during the course of the three treatment sessions until discharge from the ICU.*

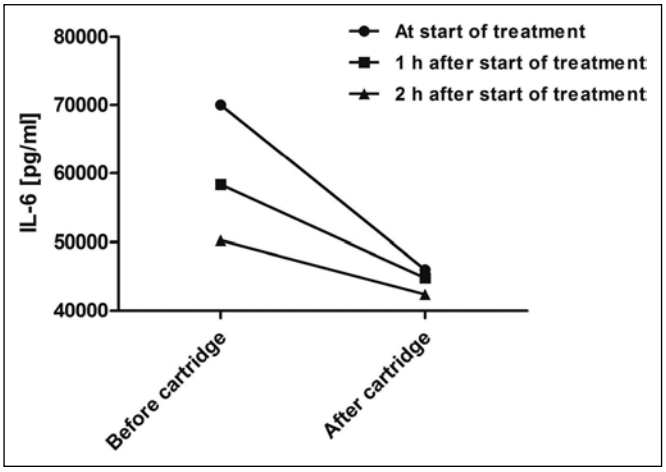

Fig. 2 - *Removal rates of IL-6 at different time points of treatment during the first session. Blood was taken before and after the CytoSorb cartridge and IL-6 levels were assessed. High levels of cytokines are reduced more efficiently than low levels pointing out the concentration-dependent autoregulatory property of the polymer.*

The general condition improved and the patient could be extubated 4 days after the third CytoSorb treatment.

CONCLUSIONS

Sepsis is often characterized by the excessive release of cytokines that can then lead to further cell death, organ damage, and finally multi-organ failure and death. Severe sepsis, where there is evidence of organ dysfunction, still has a mortality of 35% (7, 8) while in septic shock, characterized by additional severe hypotension despite fluid resuscitation, mortality rates rise as high as 60% to 80%. To date, with the exception of antibiosis and infectious source control, there is no specific therapy for sepsis and treatment consists primarily of supportive care therapies (hemodynamic stabilization, renal replacement therapy, mechanical ventilation) when needed. Several attempts have been made to modulate an uncontrolled immune response involving a multitude of mediators (e.g., cytokines, chemokines, complement components, platelet-activating factor, leukotrienes, thromboxanes). However, due to the rather complex and multifaceted nature of clinical sepsis, it becomes obvious that the modulation of the inflammatory response by targeting only a single component such as TNFα, IL-1RA or endotoxin (and despite experimentally promising data) led to failing or even devastating study outcomes in the past (9-11). Thus, blood purification techniques using diverse approaches (high-volume hemofiltration, hemoadsorption, coupled plasma filtration adsorption, high-cutoff hemofiltration/

hemodialysis) have evolved towards a more nonspecific, broad-spectrum, and concentration-dependent removal of inflammatory mediators.

Several animal studies and preliminary data from a clinical trial in severe-sepsis-patients indicate that hemoadsorption using CytoSorb™ might be beneficial in attenuating the inflammatory response during sepsis and improve outcomes. In a rat model of endotoxemia and intra-abdominal polymicrobial sepsis induced by cecal ligation and puncture hemoadsorption, the use of CytoSorb resulted in a marked reduction of key cytokines such as TNFα, IL-1β, IL-6, and IL-10, and a significant improvement of hemodynamics and short-term survival (12, 13). Interestingly, in a long-term rat model of cecal ligation and puncture (7 days), treatment with CytoSorb without direct reduction of plasma cytokine levels resulted in less sepsis-associated organ injury and a decrease in mortality from 65% in control to 40% in CytoSorb-treated animals. The authors concluded that clinical effects of hemoadsorption using CytoSorb involve mechanisms other than solely reduction of commonly measured circulating cytokines like TNFα, IL-1β (14). Noteworthy, the animal model used by Peng and colleagues closely mimics the clinical situation how patients present at the hospital with distinctive signs of systemic inflammation and a fully activated cytokine response.

The patient described in this report exhibited signs of full-blown septic shock fulfilling all sepsis criteria in the early post-operative phase. Despite immediate antibiosis, vasopressor and volume therapy, the patient developed acute renal failure and acute respiratory distress syndrome associated with a massive IL-6 response. Several lines of evidence suggest that IL-6 plasma concentration reflects severity of the disease and predicts outcome (15-18). In addition, it is the persistence of IL-6 levels in blood rather than the peak levels *per se* that correlates with disease severity and outcome (19). Due to massive IL-6 levels and the progressive worsening of the patient's condition we decided to apply CytoSorb, which eventually resulted in a significant attenuation of systemic inflammation, with reduction of IL-6 plasma levels from 70 000 pg/ml before initiation of CytoSorb treatment to 66 pg/ml after the last treatment. Despite the necessity of enucleation, we were able to successfully stabilize the patient until control of the surgical infectious source was achieved.

We cannot say whether conservative treatment (i.e., antibiotics, stabilization of hemodynamics using vasopressors and fluid, source control) would have resulted in a similar course. To test this, a controlled study with matched patients comparing conservative treatment alone with conservative treatment plus CytoSorb would have to be conducted. Therefore, a limitation of the study is that the case we describe is not representative and further studies are strongly needed. However, as the patient exhibited signs of manifest septic shock we did not want to take the risk of improvising in this situation and decided that it was better to treat with the best combination of therapies that we had at the time. Another limitation is that we only measured IL-6 as surrogate for the magnitude of the inflammatory response. In further studies, it would be interesting to analyze a panel of mediators involved in the inflammatory response to better understand the effects of the procedure and to guide treatment.

To the best of our knowledge, this case is the first report on the clinical application of CytoSorb hemoadsoption in a patient with severe sepsis and septic shock. Treatment was well tolerated and could be continuously run in combination with CVVHD and regional citrate anticoagulation for up to 36 h without any adverse events. Hemoadsoption using CytoSorb therefore seems to represent a promising approach for an effective and safe treatment of severe sepsis and septic shock.

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Conflict of Interest: None of the authors have any conflicts of interests associated with this report.

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