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Cytokine adsorption as a promising option for septic shock and multiple organ failure due to Candida infection and decompensated type 1 diabetes mellitus

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Abstract

Type 1 diabetes mellitus (T1DM) represents one of the most common chronic diseases in childhood. It is associated with high morbidity and mortality rates due to metabolic dysregulation, immunosuppressive effects, and a predisposition to fungal infections. Candidiasis is a severe infection and its prevalence has increased throughout the last decades. We report the case of a 19-year-old female patient admitted to our intensive care unit with T1DM and Candida infection associated with severe metabolic acidosis. In the absence of response to high dose catecholamine cardiovascular therapy and the presence of severe metabolic acidosis, a CytoSorb cartridge was implemented into the extracorporeal dialysis circuit resulting in a stabilization of hemodynamics accompanied by a tremendous decrease in vasopressor requirements, control of the hyperinflammatory response, as well as a resolution of metabolic acidosis and regeneration of renal function. Treatment with CytoSorb was safe and feasible without technical problems. Notably, this is the first case description reporting on the effects of CytoSorb in a patient with Candida infection as part of T1DM.

KEYWORDS

Candida, CytoSorb, hemoadsorption, multiple organ failure, type 1 diabetes mellitus

1 | INTRODUCTION

Candida is by far the most common fungal blood stream pathogen.[1] Candidemia and invasive candidiasis are major causes of morbidity and mortality, and their incidence is increasing because of the growing complexity of critically ill patients.[2] Recognition and treatment of this infection is frequently delayed with dramatic clinical deterioration.[3]

Apart from that, type 1 diabetes mellitus (T1DM) represents one of the most common chronic diseases in childhood. The disease is accompanied by high morbidity and mortality rates due to a metabolic dysregulation, its immunosuppressive effects and a predisposition of these patients to fungal infections, particularly candida yeast species.[4,5]

Therefore, the combination of both diseases (ie, Candida infection and T1DM) carries a high risk for the development of bloodstream infections and if left untreated, this can result in sepsis or its most severe form septic shock.

Both represent life-threatening syndromes induced by a dysregulated immune response to infections and are connected to high rates of morbidity and mortality especially among critically ill patients.[6] High cytokine levels related to an overwhelming immune response of the organism as well as the refractory hypotension play a crucial role for the

dysfunction of the cardiovascular system.[7] The hemodynamic instability implies ischemic tissue damage as a result of hypoperfusion and inflammation. Extended vasopressor requirement is reported to correlate with vascular failure, metabolic dysregulation, and acute renal failure and is known to be associated with increase of mortality during sepsis.[8]

In this context, the reduction of cytokine blood levels by means of extracorporeal hemoadsorption represents a novel strategy to control the overwhelming immune response in the early phase of septic shock with cardiovascular dysfunction. Owing to the improvement of vasopressor efficacy, the stabilization of hemodynamic conditions is reported to be beneficial for patients suffering from septic shock with multiple organ failure. CytoSorb has been applied in many patients suffering from various diseases and is reported to reduce high cytokine plasma levels effectively.[9–14] We herein report the case of a 19-year-old female patient with T1DM and Candida infection associated with severe metabolic acidosis admitted to our intensive care unit, who was successfully treated with CytoSorb hemoperfusion in combination with continuous renal replacement therapy (CRRT).

2 | CASE DESCRIPTION

A 19-year-old female patient with severe metabolic acidosis and coma (GCS 4) was admitted to the intensive care unit. Acid–base analysis revealed a severe metabolic acidosis with advanced electrolyte disturbances (pH < 6.7; pCO_2 = 2.8 kPa; pO_2 = 22 kPa; SpO_2 = 98%; HCO_3 = 3.7 mmol/L; BE = −32.6). Additionally, high infection parameters, hyperkalemia, elevated retention parameters as well as acute renal failure (AKIN III according to KDIGO) were observed. Sedation, protective intubation, and mechanical ventilation were performed and a Shaldon catheter was inserted.

In the state of septic shock, circulatory stabilization including high-dose catecholamine support, balanced volume therapy, hydrocortisone, and buffering with $NaHCO_3$ and THAM was administered. Antibiotic therapy was initially performed by the administration of meronem (meropenem, Merck & Co., Kenilworth, NJ, USA). Since *Candida dubliniesis* aerobic and *Candida albicans* could be detected in blood cultures, antibiotic therapy was completed with cancidas (caspofungin, Merck & Co.).

Given that metabolic acidosis and increased retention parameters persisted, continuous renal replacement therapy (CRRT) was initiated within 24 hours of admission. Due to her advanced hemodynamic instability despite high-dose catecholamine therapy and due to significant elevated IL-6 levels (>1000 pg/mL), a CytoSorb 300 adsorber (CytoSorbents Europe, Berlin, Germany) was additionally implemented.

We performed one treatment session with CytoSorb for 20 hours. The CytoSorb 300 adsorber was installed post-hemofilter into the CRRT circuit (Prismaflex, Baxter Deutschland, Unterschleißheim, Germany). Treatment was carried out in CVVHD mode with citrate as anticoagulation at a blood flow rate of 100–150 mL/min.

The combined application of both therapeutic procedures was associated with a resolution of metabolic acidosis. Hemodynamics stabilized and vasopressor support could be reduced and finally stopped during the treatment interval. Hyperinflammation could be rapidly controlled and all inflammatory parameters were reduced during the course of treatment (Table 1). Additionally, treatment resulted in a reduction of retention parameters and an overall regeneration of renal function as evidence by a return of spontaneous diuresis to normal levels. Initial i.v. insulin therapy was changed to a subcutaneous regimen due to moderate blood sugar levels (8–12 mmol/L).

The patient was transferred to the internal ward 9 days after admission. Due to appropriate handling, the treatment with CytoSorb was safe and feasible without technical problems.

3 | DISCUSSION

Several studies have reported the impact of cytokine adsorption by extracorporeal CytoSorb therapy on an improvement in hemodynamics and metabolic variables among critically ill patients.[15,16] CytoSorb treatment was reported to be highly effective if started within 24 hours of sepsis diagnosis.[17]

The aforementioned patient suffered from a severe metabolic acidosis due to Candida infection as part of T1DM, which resulted in septic shock and multiple organ failure. The combination of CytoSorb hemoadsorption and CRRT was started within 24 hours from sepsis diagnosis and resulted in improved renal function, significantly improved hemodynamics including reduction of catecholamine therapy, and a resolution of severe ketoacidosis (Table 1). In addition, therapy led to a general improvement in the patient's clinical condition. Therefore, no follow-up IL-6 measurement was performed.

Weingold et al suggested IL-6 to be necessary for the induction of the CRP gene. Our findings are in concordance with their assumption inasmuch as an increase of IL-6 was associated with an increase of CRP.[18]

Simoni recently discussed the role of CytoSorb for sepsis and septic shock.[19] Inter alia, he mentioned Malard et al who described this device as "unable to remove endotoxins."[20] Feri already discussed the limitations of these in vitro experiments.[21] Whereas the CytoSorb adsorber has been originally marketed for the removal of excess cytokine blood levels, its effects seem to reach far beyond this and there is growing evidence that the adsorption properties also enable the removal of pathogen-associated molecular pattern molecules

TABLE 1 Clinical parameters

	Parameter	Units	Reference	Day 1		Day 2			Day 3		Day4	
				before CytoSorb therapy		CytoSorb treatment session			after CytoSorb therapy			
Catecholamine demand	Norepinephrine	µg/kg/min		0.4	0.8	0.9	0.3	0.2	0.1	0.075	0.05	0
Hemodynamics	Mean arterial pressure	mmHg	70–100	40	55	55	50	60	80	80	90	90
Inflammatory variables	C-reactive protein	mg/L	<3.0	38.50								
	Procalcitonin	ng/mL	<0.06	74.24			38.86					7.17
	Leukocytes	$*10^9/\mu L$	3.9–10.2	38.49	15.80		11.50			10.17		6.40
	IL-6	ng/mL	<100		>1000							
Renal variables	Creatinine	µmol/L	53–88	427	312		294			217		155
Metabolic variables	pH			6.65	6.69	7.10	7.31	7.36	7.38	7.41	7.39	7.43
	Lactate	mmol/L	0.5–2.2	2.40	2.1	1.59	1.37	1.02		1.3		0.97
	Base excess	mmol/L	−2.0–2.0	−32.60	−31.70	−20.7	−10.70	2.1		1.9		2.0
	HCO_3^-	mmol/L	21.5–25.5	3.7	3.7	8.2	15.9	26.4		25.4		26.1
	Potassium	mmol/L	3.4–4.4	8.9	6.7	4.5	4.0			3.6		3.5
	Glucose	mmol/L	4.11–5.89	67.18		26.7	21.7	16.3		13.2		14.3

(PAMPS), such as bacterial exotoxins, as well as damage-associated molecular pattern molecules (DAMPS).[22] In this regard, CytoSorb might have also helped to lower the pathogenic burden by the removal of bacterial exotoxins as well as mycotoxins in addition to other inflammatory relevant parameters resulting in an attenuation of the inflammatory response in our patient.

Little data is available regarding the removal of anti-infective drugs during treatment with CytoSorb. Besides a recently published in vitro attempt by König et al who quantified the adsorptive capacity of various commonly used antibiotic and antimycotic drugs, also Reiter et al investigated this important topic.[23,24] To our knowledge, nothing is known about the clearance of further drugs particularly like cancidas (caspofungin). Moreover, the use of CytoSorb in vivo regarding the adaptation of drug administration should be considered in further investigations. Of note, this is the first case description reporting on the effects of CytoSorb in a patient with Candida infection as part of T1DM.

The attenuation of the overwhelming inflammatory response in systemic inflammatory diseases can effectively be controlled by the application of CytoSorb resulting in improved clinical outcomes. As Simoni recently mentioned, CytoSorb among other devices "showed a limited ability to significantly improve the outcomes, their positive role in the treatment of septic shock patients remains undisputed."[19]

With regard to our results, there is a need to perform prospective randomized controlled studies to appropriately assess the diverse effects as well as to optimize the therapeutic procedures of this tool beyond the context of sepsis or septic shock. Various peculiarities of other diseases for example, cardiogenic shock[25] or focal segmental glomerulosclerosis (FSGS)[26] etc., have to be taken into consideration as well.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Concept, Data collection, Data interpretation, Drafting article, Critical revision of article: GK
Critical revision of article, Approval of article: MBS
Data interpretation, Critical revision of article: AM

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REFERENCES

1. Arendrup MC. Candida and candidaemia. Susceptibility and epidemiology. Dan Med J. 2013;60(11):B4698.
2. Antinori S, Milazzo L, Sollima S, Galli M, Corbellino M. Candidemia and invasive candidiasis in adults: a narrative review. Eur J Intern Med. 2016;34:21–8.

3. Epelbaum O, Chasan R. Candidemia in the intensive care unit. Clin Chest Med. 2017;38(3):493–509.
4. Soni AP, Astekar M, Metgud R, Vyas A, Ramesh G, Sharma A, et al. Candidal carriage in diabetic patients: a microbiological study. J Exp Ther Oncol. 2019;13(1):15–21.
5. Lipton RB, Drum M, Burnet D, Rich B, Cooper A, Baumann E, et al. Obesity at the onset of diabetes in an ethnically diverse population of children: what does it mean for epidemiologists and clinicians? Pediatrics. 2005;115(5):e553–60.
6. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
7. Mackenzie I. The haemodynamics of human septic shock. Anaesthesia. 2001;56(2):130–144.
8. Dünser MW, Ruokonen E, Pettilä V, Ulmer H, Torgersen C, Schmittinger CA, et al. Association of arterial blood pressure and vasopressor load with septic shock mortality: a post hoc analysis of a multicenter trial. Crit Care. 2009;13(6):R181.
9. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Early Goal-Directed Therapy Collaborative Group, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.
10. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2004;30(4):536–55.
11. Mitzner SR, Gloger M, Henschel J, Koball S. Improvement of hemodynamic and inflammatory parameters by combined hemoadsorption and hemodiafiltration in septic shock: a case report. Blood Purif. 2013;35(4):314–5.
12. Hetz H, Berger R, Recknagel P, Steltzer H. Septic shock secondary to ß-hemolytic streptococcus-induced necrotizing fasciitis treated with a novel cytokine adsorption therapy. Int J Artif Organs. 2014;37(5):422–6.
13. Born F, Pichlmaier M, Peterss S, Khaladj N, Hagl C. Systemic inflammatory response syndrome in der Herzchirurgie: Neue Therapiemöglichkeiten durch den Einsatz eines Cytokin-Adsorbers während EKZ. Kardiotechnik. 2014;41–46.
14. Kellum JA, Song M, Venkataraman R. Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. Crit Care Med. 2004;32(3):801–5.
15. Friesecke S, Stecher SS, Gross S, Felix SB, Nierhaus A. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. Artif Organs. 2017;20:252–9.
16. Hawchar F, Lasulo I, Oveges N, Trasy D, Ondrik Z, Molnar Z. Extracorporeal cytokine adsorption in septic shock: a proof of concept randomized, controlled pilot study. J Crit Care. 2019;49:172–8.
17. Kogelmann K, Jarczak D, Scheller M, Drüner M. Hemoadsorption by CytoSorb in septic patients: a case series. J Crit Care. 2017;21(1):74.
18. Weinhold B, Rüther U. Interleukin-6-dependent and -independent regulation of the human C-reactive protein gene. Biochem J. 1997; 327(Pt 2):425–9.
19. Simoni J. Why do we need extracorporeal blood purification for sepsis and septic shock? Artif Organs. 2019;43:444–7.
20. Malard B, Lambert C, Kellum JA. In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. Intensive Care Med Exp. 2018;6:12.
21. Feri M. "In vitro comparison of the adsorption of inflammatory mediators by blood purification devices": a misleading article for clinical practice? Intensive Care Med Exp. 2019;7(1):5.
22. Gruda MC, Ruggeberg K-G, O'Sullivan P, Guliashvili T, Scheirer AR, Golobish TD, et al. Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. PLoS ONE 2018;13(1):e0191676.
23. König C, Röhr AC, Frey OR, Brinkmann A, Roberts JA, Wichmann D, et al. In vitro removal of anti-infective agents by a novel cytokine adsorbent system. Int J Artif Organs. 2019;42(2):57–64.
24. Reiter K, Bordoni V, Dall'Olio G, Ricatti MG, Soli M, Ruperti S, et al. In vitro removal of therapeutic drugs with a novel adsorbent system. Blood Purif. 2002;20(4):380–8.
25. De Schryver N, Hantson P, Haufroid V, Dechamps M. Cardiogenic shock in a hemodialyzed patient on flecainide: treatment with intravenous fat emulsion, extracorporeal cardiac life support, and CytoSorb® hemoadsorption. Case Rep Cardiol. 2019; 2019:1–5. eCollection:1905871.
26. Schenk H, Müller-Deile J, Schmitt R, Bräsen JH, Haller H, Schiffer M. Removal of focal segmental glomerulosclerosis (FSGS) factor suPAR using CytoSorb. J Clin Apher. 2017;32(6):444–52.

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