A New Therapeutic Strategy for Streptococcal Toxic Shock Syndrome: A Key Target for Cytokines

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Abstract

We searched for innovative treatments specifically targeted to the cytokines of three critically ill patients with streptococcal toxic shock syndrome (STSS). Direct hemoperfusion with polymyxin B-immobilized fiber improved the hemodynamics in all three patients who had developed shock at presentation. Continuous hemodiafiltration coupled with plasma exchange for simultaneous removal of several mediators of the inflammatory cascade improved outcome in case 2 and lessened the aggressive clinical course and prolonged survival in case 3. The application of these technologies appears to open new and interesting therapeutic options and may lead to improved survival in STSS.
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Key words: continuous hemodiafiltration, direct hemoperfusion, polymyxin B-immobilized fiber, plasma exchange, inflammatory cascade

Introduction

Group A streptococci (GAS) are responsible for a wide spectrum of clinical illnesses, ranging from milder and more easily treatable infections such as pharyngitis, impetigo, and pyoderma to severe invasive disease, referred to as streptococcal toxic shock syndrome (STSS). The emergence of severe GAS infection since the 1980s has now been reported from most parts of the world (1–10).

STSS, an acute, progressive, and often fatal illness appears to be related to an overall change in the virulence of GAS and the reappearance of highly mucoid exotoxin-producing strains. Strains of GAS isolated from patients with STSS have been predominantly of M types 1 and 3, which produce either pyrogenic exotoxin A or B or both (1, 3–10). These streptococcal pyrogenic exotoxins (Spes) have been the subject of much attention because of their biological activity (11–14). They act as superantigens and induce the proliferation of T lymphocytes in vitro and the synthesis and release of several cytokines in vivo, including tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), and interleukin-6 (IL-6). The production of these exotoxins is associated with a marked febrile response, alteration of membrane permeability, and enhancement of host susceptibility to the lethal shock of endotoxin.

The pathogenic mechanisms of shock, multiple-organ failure, and tissue destruction in STSS are not fully understood, and there is about 30–50% mortality in patients with STSS despite several possibly feasible treatments consisting of surgical debridement, intravenous fluids, appropriate antibiotics, and intravenous immunoglobulin. Here, we report 3 cases of STSS and suggest a new therapeutic strategy for STSS emphasizing a key target for the cytokines.

Case Reports

Case 1

A 77-year-old woman undergoing hemodialysis (HD) for 10 years was referred with intractable lumbago and severe pain in the left thigh on June 28, 2000. The underlying disease of chronic renal failure was unknown. She had a past history of impetigo 4 years earlier. Initial examination was remarkable with a temperature of 36.0°C, a pulse rate of 108 beats per minute, systolic blood pressure at <60 mmHg, a respiratory rate of 28 beats per minute and her mental status was drowsy. Shock was apparent. Her left thigh was erythematous and swollen. Bacterial blood cultures were positive for *Streptococcus pyogenes* and thus immediate intravenous antibiotic therapy (imipenem/cilastatin; IPM/CS at a daily dose of 2 g and sultamicillin; ABPC/SBT at a daily dose of 12 g) and intravenous immunoglobulin (IVIG) at a

Table 1. Laboratory Data at Admission in Cases 1, 2 and 3

	Case 1		Case 2		Case 3
WBC	18,020/mm^3	WBC	9,020/mm^3	WBC	15,680/mm^3
RBC	299×10^4/mm^3	RBC	392×10^4/mm^3	RBC	491×10^4/mm^3
Hb	9.0 g/dl	Hb	13.0 g/dl	Hb	16.3 g/dl
Plt	7.3×10^4/mm^3	Plt	13.1×10^4/mm^3	Plt	14.5×10^4/mm^3
CRP	13.2 mg/dl	CRP	16.2 mg/dl	CRP	35.1 mg/dl
AST	31 IU/l	AST	37 IU/l	AST	274 IU/l
ALT	20 IU/l	ALT	28 IU/l	ALT	119 IU/l
LDH	244 IU/l	LDH	269 IU/l	LDH	115 IU/l
CPK	221 IU/l	CPK	274 IU/l	CPK	12,523 IU/l
TP	4.3 g/dl	TP	4.3 g/dl	TP	5.6 g/dl
Alb	2.6 g/dl	Alb	2.7 g/dl	Alb	2.8 g/dl
Cr	6.3 mg/dl	Cr	1.0 mg/dl	Cr	5.3 mg/dl
BUN	55 mg/dl	BUN	20 mg/dl	BUN	83 mg/dl
Na	135 mEq/l	Na	131 mEq/l	Na	142 mEq/l
K	3.4 mEq/l	K	3.5 mEq/l	K	4.2 mEq/l
Cl	98 mEq/l	Cl	103 mEq/l	Cl	108 mEq/l
β-D glucan	225.7 pg/ml	β-D glucan	2.2 pg/ml	β-D glucan	2.38 pg/ml
Endotoxin	<1.81 pg/dl	Endotoxin	5.85 pg/dl	Endotoxin	5.41 pg/dl
Blood gas	(room air)	Blood gas	(room air)	Blood gas	(room air)
pH	7.268	pH	7.557	pH	7.346
pCO$_2$	31.2 Torr	pCO$_2$	17.0 Torr	pCO$_2$	21.7 Torr
pO$_2$	68.5 Torr	pO$_2$	113.2 Torr	pO$_2$	68.9 Torr
HCO$_3$	13.8 mmol/l	HCO$_3$	15.2 mmol/l	HCO$_3$	11.6 mmol/l

daily dose of 5 g were initiated. Laboratory data at admission are presented in Table 1. The level of TNFα was markedly elevated (Fig. 1). Despite the initial appropriate therapy with cathecolamines, hemodynamic instability and respiratory failure ensued. Mechanical ventilation was necessary due to the severity of acute respiratory distress syndrome (ARDS). Direct hemoperfusion (DHP) with polymyxin B-immobilized fiber (PMX) (Toraymixin, Toray Medical Inc., Tokyo, Japan) was performed for 2 hours in order to maintain the hemodynamics although endotoxin was not detected. Blood in the extracorporeal circuit was anticoagulated with nafamostat mesilate (Futhan, Torii, Tokyo, Japan). Blood flow (Qb) was controlled at 60 ml/min by a roller pump. After DHP with PMX followed by improvement of the hemodynamics, intermittent hemodiafiltration (IHDF) was started for 4 hours. Conditions for IHDF were adjusted as follows: Qb; 100 ml/min, dialysate flow (Qd), 500 ml/min; replacement fluid; Subblood-B (Shimizu Inc., Kyoto, Japan) containing sodium, 140.0 mEq/l; potassium, 2.0 mEq/l; chloride, 111.0 mEq/l; calcium, 3.5 mEq/l; magnesium, 1.0 mEq/l; bicarbonate, 35.0 mEq/l; and glucose, 100.0 mg/dl; dialyzer, PS-1.3 (polysulfone membrane with 1.3 m^2 surface area, Toray Medical Inc.) and an individualized bedside console, model DBG-01 (Nikkiso Co., Tokyo, Japan). Despite maximal supportive therapies, she developed hepatic failure and died 27 hours after admission. At autopsy, extensive muscular necrosis and necrotizing fasciitis was evident in the buttock and thigh.
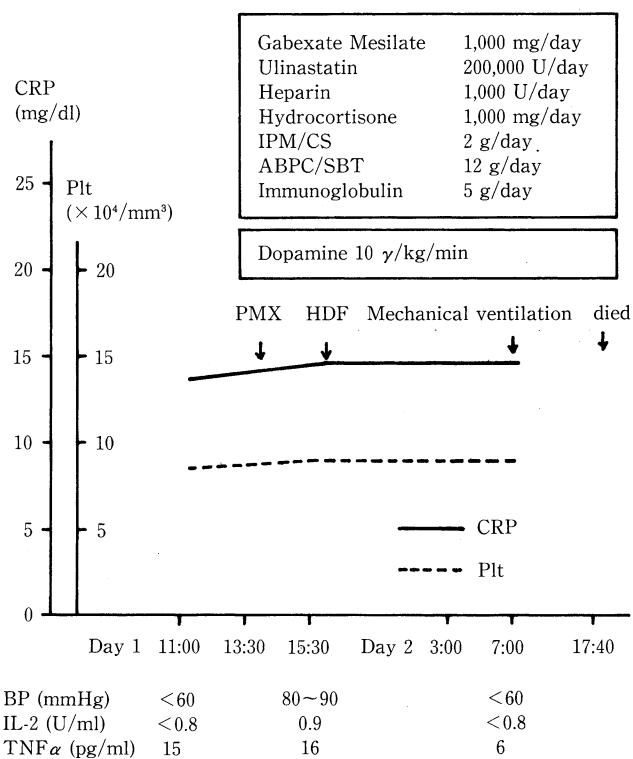

Figure 1. Clinical course of case 1. TNFα remained elevated despite DHP with PMX and IHDF which might be associated with aggressive clinical course. BP: blood pressure, Plt: platelet, PMX: polymyxin B-immobilized fiber, HDF: hemodiafiltration.

Case 2

A 35-year-old woman was referred with severe pain in left thigh and buttock and high grade fever mimicking pelvic inflammatory disease on June 26, 2001. She had a past history of anorexia nervosa 4 years earlier. Initial examination was remarkable with a temperature of 36.5°C, a pulse rate of 122 beats per minute, blood pressure at 72/50 mmHg, a respiratory rate of 20 beats per minute, and her mental status was drowsy. Shock was apparent. Her left thigh was erythematous and swollen (Fig. 2A). A generalized erythematous macular rash subsequently developed. Magnetic resonance image (MRI) revealed an inflammatory lesion in her left thigh (Fig. 3). Extensive debridement of her left thigh was performed twice (Fig. 2B); necrosis extended to the fascia, but not to the muscle with culture revealing *Streptococcus pyogenes* and *Psedomonas aeruginosa*. Bacterial blood cultures were only positive for *Streptococcus pyogenes* and so immediate intravenous antibiotic therapy (meropenem; MEMP at a daily dose of 2 g, ABPC/SBT at a daily dose of 12 g, and clindamycin at a daily dose of 1,200 mg) and IVIG at a daily dose of 5 g were initiated. Laboratory data at admission are presented in Table 1. The serum creatinine kinase (CPK) level was normal, and surgical exploration confirmed that the muscle was not infected. The levels of IL-6 (Fig. 4) and endotoxin were remarkably elevated which suggested co-infection with gram-negative bacteria. Despite the initial appropriate therapy, anuria and acute renal failure ensued. To perform DHP with PMX, venovenous vascular access was achieved with a flexible double-lumen catheter via the right femoral vein. Two hours DHP was performed on the first day and the next day. Plasma exchange (PE) was also performed twice in which conditions were adjusted as follows: Qb, 50 ml/min; replacement fluid, 3 *l* of fresh frozen plasma (FFP); dialyzer, Plasmaflow (Asahi Medical Inc.); and an individualized bedside console, Plasauto 2500 (Asahi Medical Inc., Tokyo, Japan). Continuous HDF (CHDF) was started on the second day of hospitalization in which conditions were adjusted as follows: Qb, 100 ml/min; Qd, 300 ml/min; replacement fluid, Subload-B; dialyzer, APF-06S (polyacrylonitrile, Asahi Medical Inc.) and an individualized bedside console, model ACH-10 (Asahi Medical Inc.). Following these therapies, hemodynamic, respiratory, and renal function parameters improved with increments of urinary output. After finishing the
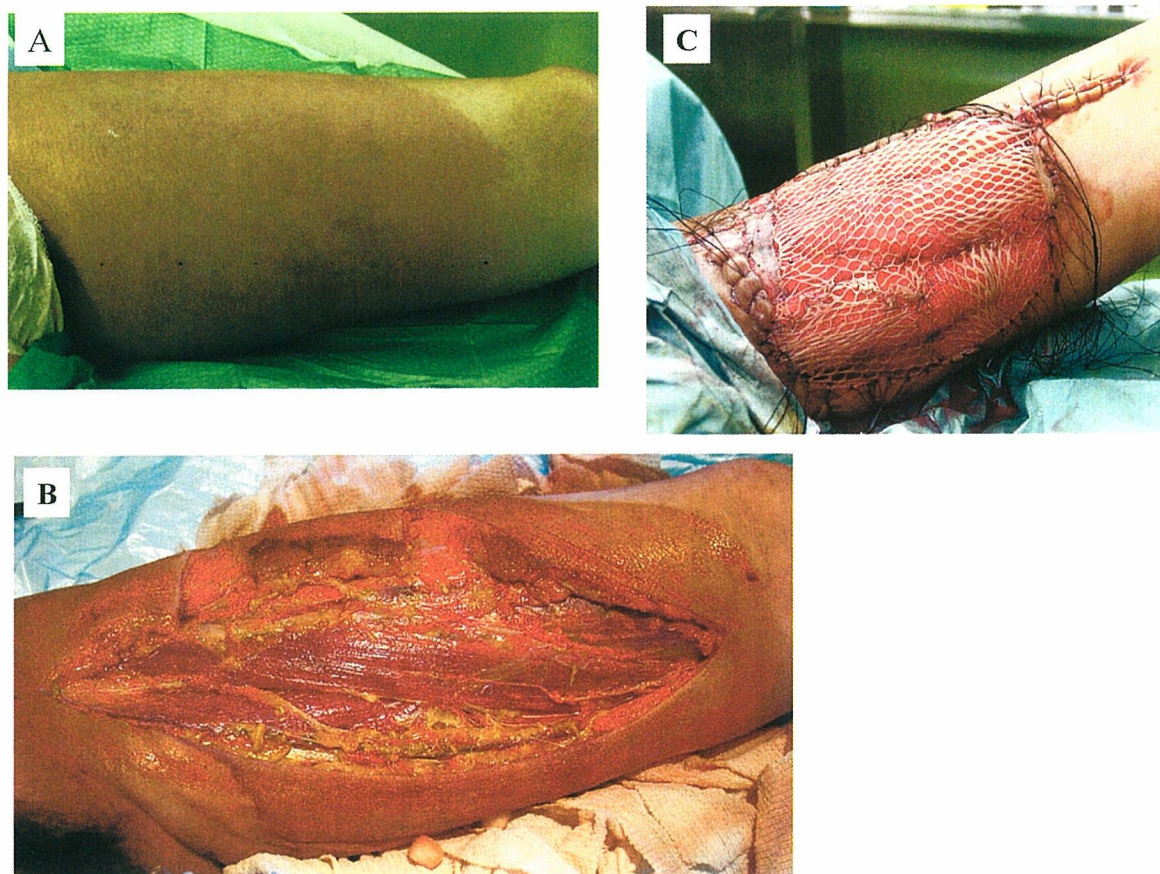

Figure 2. Photographs of case 2 show (A) erythematous and swollen thigh, (B) extensive debridement, and (C) autografted skin.
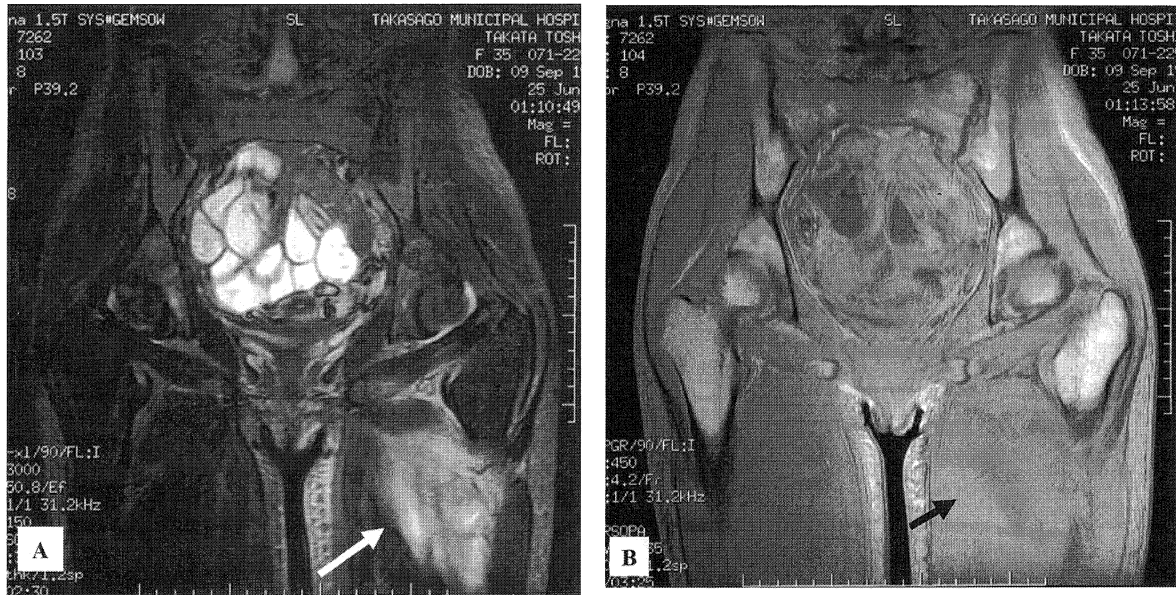
Figure 3. Magnetic resonance image (MRI) of case 2. (A) T1-weighted MRI showing high signal intensities (arrow), and (B) T2-weighted MRI showing low signal intensities (arrow) in the left thigh.

course of antibiotics, the patient remained afebrile with good wound healing and integrity by skin autografts (Fig. 2C).

Case 3

A previously healthy 63-year-old man was referred with shock and high grade fever, preceded by the local soft tissue trauma in his right thigh after a bicycle accident two days previously on August 16, 2001. Initial examination was remarkable with a temperature of 37.3°C, a pulse rate of 143 beats per minute, blood pressure at 80/40 mmHg, a respiratory rate of 24 beats per minute, and his mental status was drowsy. Shock was apparent and mechanical ventilation was necessary at admission. His right thigh was erythematous and necrotic with vesicles and bullae (Fig. 5A, B). A generalized erythematous macular rash subsequently developed. Extensive debridement of his left thigh was performed (Fig. 5C); necrosis extended to the fascia and muscle with culture revealing *Streptococcus pyogenes*. Bacterial blood cultures were positive for *Streptococcus pyogenes*. He fulfilled all the proposed case definition criteria for the diagnosis of definitive STSS (2). Based on the treatment of case 2, immediate intravenous antibiotic therapy (2 g of MEMP, 12 g of ABPC/SBT, and 2,400 mg of clindamycin), IVIG at a daily dose of 5 g, DHP with PMX, PE, and CHDF were initiated. Laboratory data at admission are presented in Table 1. The levels of CPK and IL-6 were markedly elevated (Fig. 6). Following these therapies, hemodynamic, respiratory, and renal function parameters improved with increments of urinary output. However, the patient remained febrile with superinfections and was malnourished with continuous protein loss from a wide area of wounds (Fig. 5D). Despite maximal supportive therapies, he died on the 24th day of hospitalization.

Discussion

Recent studies show an increasing incidence of gram-positive sources of sepsis (15), and it is possible that these cases may predominate in the coming years. It appears that gram-positive organisms may also be more virulent in aggravating the disease, as can be evidenced by the emergence of STSS (1–10). This may result from the ability of gram-positive organisms to produce more inflammation-causing cell wall constituents such as peptidoglycan and lipoteichoic acid, as well as unbound exotoxins. A single component of gram-negative organism (endotoxin) is believed to be involved in inciting sepsis (16). Endotoxin is relatively easy to purify and inject, and, because it is a single substance, the mechanisms by which gram-negative organisms cause sepsis can be mapped fairly simply. In contrast, a gram-positive organism contains a number of different substances that can initiate sepsis.

The approaches to therapy include surgical debridement, appropriate antibiotics (17) and intravenous immunoglobulin (18–20), and the resulting mortality has remained largely unchanged for over 20 years in STSS (1, 4–10). The type and extent of tissue injury, systemic toxicity, and multiorgan system failure appear to be mediated by Spes via the induction of biologically potent endogenous cytokines (1–10). Indeed, the constellation of renal failure, shock, hypocalcemia, and thrombocytopenia is similar to that seen in staphylococcal
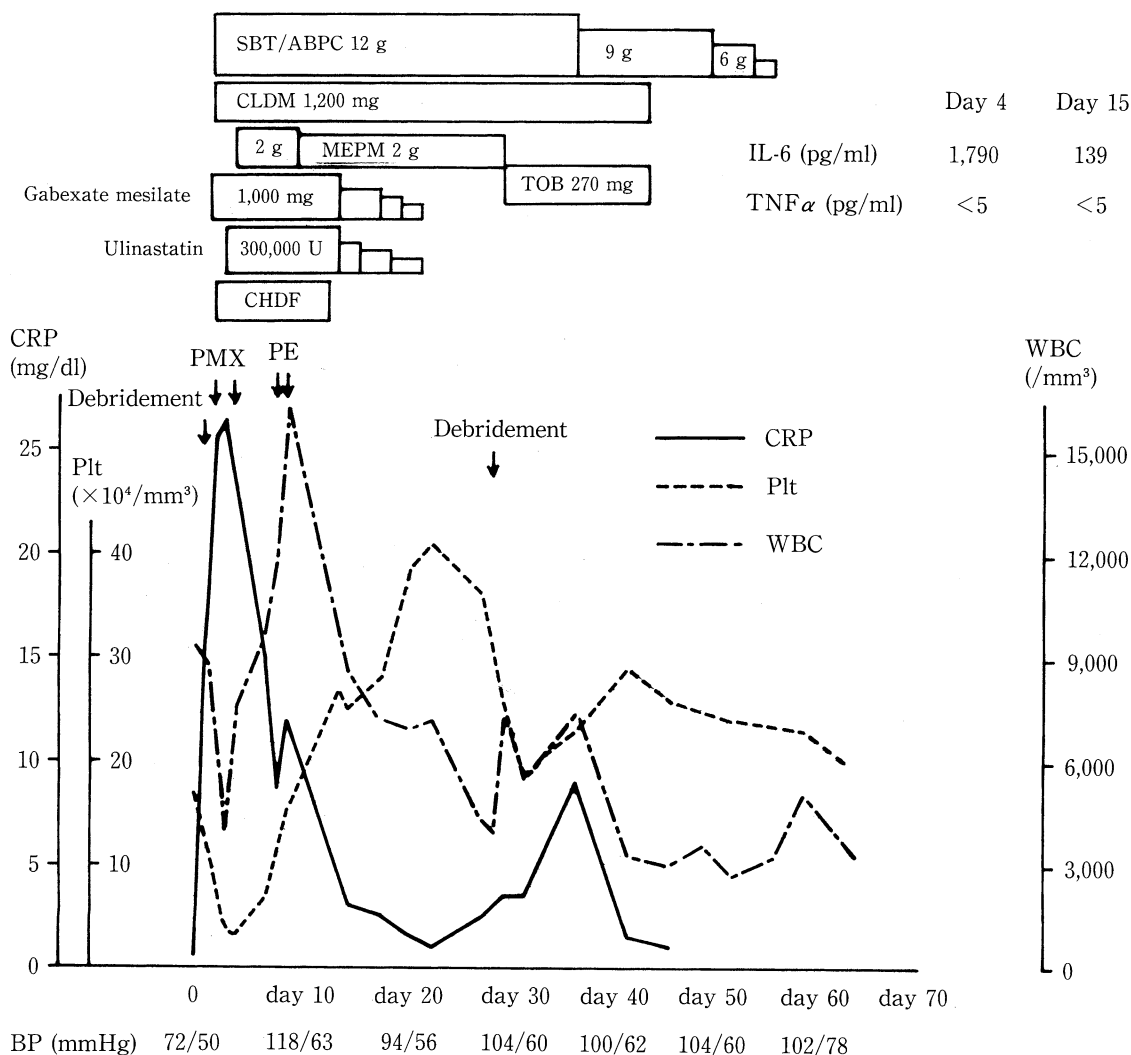
Figure 4. Clinical course of case 2. Intensive therapies caused a significant attenuation of the inflammatory signs and improvement of thrombocytopenia. IL-6 levels decreased and blood pressure improved with increments of urinary output successfully with CHDF coupled with DHP, PMX and PE. DHP, direct hemoperfusion; PMX: polymyxin B-immobilized fiber, CHDF: continuous hemodiafiltration, PE: plasma exchange, Plt: platelet, BP: blood pressure.

toxic shock syndrome, which is clearly a toxin-mediated illness. Spes could mediate this clinical derangement, shared with toxic shock syndrome toxin-1, which includes the following: pyrogenicity, enhancement of susceptibility to endotoxin shock, enhancement of delayed hypersensitivity to induced skin rashes, cytotoxicity (including cardiac damage), mitogenicity (nonspecific) for T lymphocytes, immunosuppression (of B-lymphocyte function), alteration of host antibody response, and mitogenic activity in humans and in lymphocytes from rabbits (11). These facts emphasize the importance of the development of multitargeted therapeutic strategies which would theoretically attempt to neutralize the toxins or the cytokines released as a consequence of the streptococcal toxins. Therefore, we searched for innovative

treatments specifically targeted to the cytokines of critically ill patients with STSS. Recent clinical trials using anti-cytokine therapy have failed to show amelioration of septic shock (21, 22). Therefore, extracorporeal therapies to reduce circulating levels of the mediators of sepsis were introduced.

The risk of death in patients with STSS increases with the need for dialytic support, but cardiovascular instability is the most common complication of dialysis. Prompt surgical intervention cannot be performed due to cardiovascular instability in patients with STSS. PMX is a biomaterial for selective absorption of endotoxin (23, 24). Multicenter uncontrolled clinical trials in Japan have shown that treatment with DHP with PMX ameliorates hyperdynamic shock (23) and decreases its effect on cytokine generation by
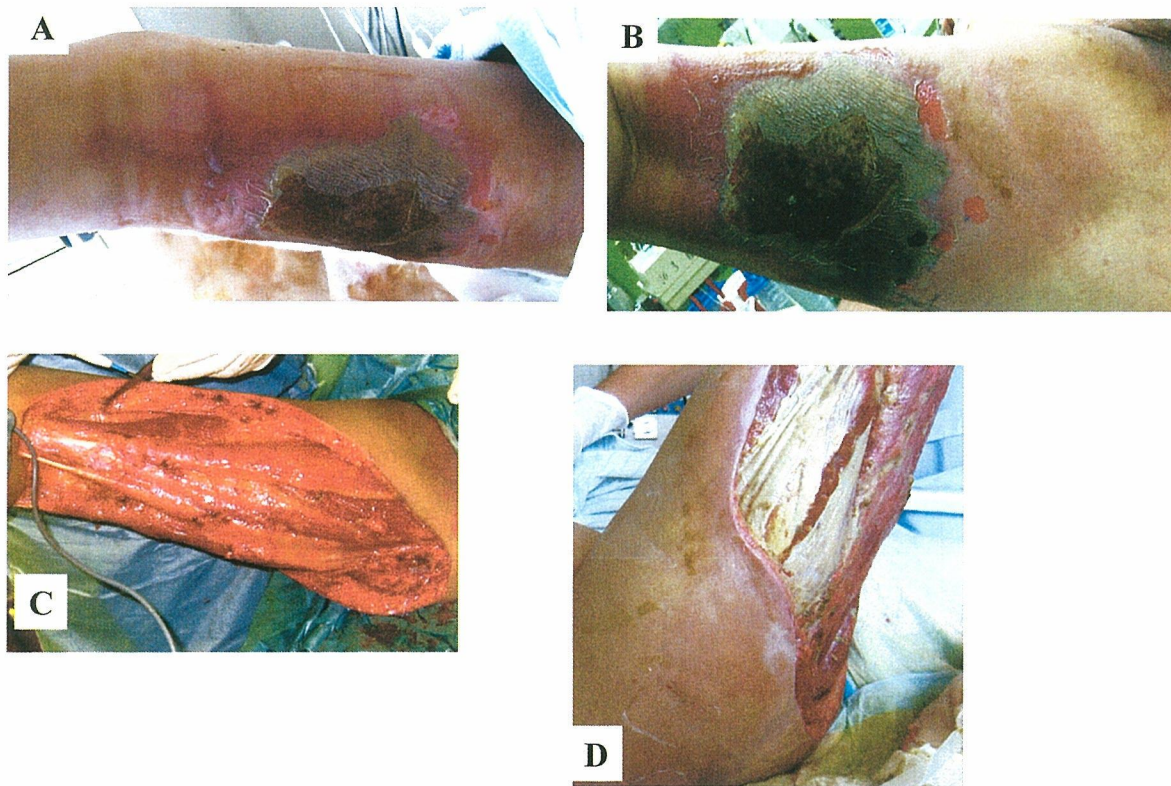
Figure 5. Photographs of case 3 show (A, B) erythematous and necrotic thigh with vesicles and bullae, (C) extensive debridement, and (D) development of the erythematous macular rash.

mononuclear cells (25), although a close relationship between the improvement in systemic hemodynamics and removal of endotoxins by DHP with PMX could not be shown. Indeed, DHP with PMX improved the hemodynamics in all 3 patients with STSS who had developed shock at presentation regardless of the level of blood endotoxins. The exact mechanism through which partial elimination of cytokines from blood stream adjusts hemodynamics could not be identified. One possible explanation may come from blocking of the synergistic interaction between Spes and endotoxins as a result of decreasing normal or physiological levels of endotoxins. Another possible explanation may be adsorption of anandamide (ANA), an endogenous cannabinoid. ANA can be generated by activated macrophages which are the pivotal cells in the signaling mechanisms, and by the resulting biological responses during septic shock; ANA is thought to be a paracrine contributor to hypotension. The adsorption of ANA by PMX (26) may abolish the diverse effects of ANA such as hypotension, immunosuppression and cytotoxicity, and may extend a new therapeutic strategy for STSS.

Several methods of dialysis for the removal of inflammatory mediators are available for renal replacement therapy (RRT) (27). IHDF increases the risk of hemodynamic instability. Indeed, cardiovascular instability followed IHDF in case 1. On the other hand, the slow nature of CHDF allows for a slow rate of ultrafiltration with a lower impact on blood pressure. CHDF may be indicated for hemodynamically unstable patients with STSS. Accumulating evidence (28) suggests that immune-enhancing enteral preparations in critically ill patients such as STSS decrease the duration of hospital stays, the number of infections and perhaps mortality because of the severe catabolic status. Nutritional management in STSS is influenced by the modality of renal support. There are some difficulties associated with increased azotemia and the fluid overload induced by administration of protein or nutrients by means of conventional dialytic techniques. In contrast, continuous fluid removal with CHDF allows infusion of large amounts of fluids and ensures adequate caloric intake.

Due to the limited capacity of filtration with CHDF, it is very unlikely to obtain significant variations in the plasma circulating levels of inflammatory cytokines. The underlying rationale is that PE facilitates the removal of higher amounts of harmful bacterial products and endogenous inflammatory mediators (29). An alternative explanation is that PE simply makes room for the liberal administration of large volumes of blood products which themselves have significant immunomodulatory effects. Drenger et al (30) described the use of PE in septic patients caused by β-hemolytic streptococcus group A. They measured the plasma concentrations of TNFα and IL-1. The levels of both mediators were
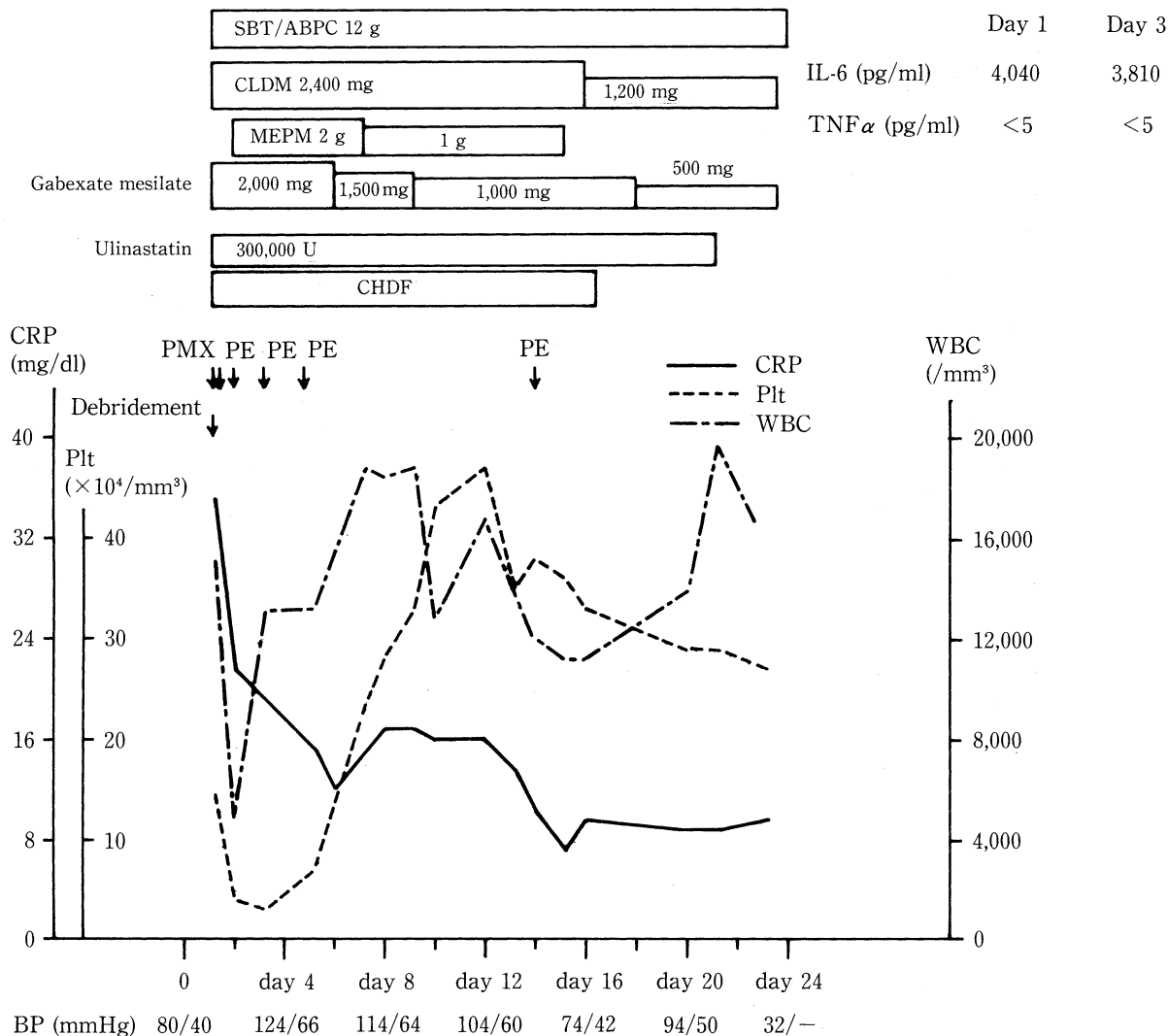
Figure 6. Clinical course of case 3. Inflammatory signs persisted and IL-6 levels remained elevated despite maximal support therapies. Blood pressure improved with increment of urinary output temporary with CHDF coupled with DHP, PMX and PE, but afterwards urinary output decreased along with continuous protein loss from wounds. DHP: direct hemoperfusion, PMX: polymyxin B-immobilized fiber, CHDF: continuous hemodiafiltration, PE: plasma exchange, Plt: platelet, BP: blood pressure.

significantly elevated at presentation and fell rapidly after PE. However, large amounts of plasma substitute and the evident cost implications may, in fact, limit the application in the treatment of STSS.

TNFα, a pleiotropic cytokine, mediates a broad spectrum of host responses to Spes. It is released from circulating and resident cells following stimulation by Spes. In case 1, the level of TNFα was elevated at presentation and remained elevated after DHP with PMX and IHDF which might be correlated with the severity and mortality of STSS. These findings suggest that removal of any toxigenic streptococcal foci is of paramount importance to suppress the synthesis of inflammatory mediators. TNFα stimulates a cascade of vasoactive and inflammatory mediators that participate in

STSS such as IL-1β and IL-6. In cases 2 and 3, the levels of IL-6 were remarkably elevated, while TNFα was not detected. The reason for the discrepancy among cytokines may be explained by the different inflammatory time course or severity. The successful removal of inflammatory mediators by CHDF coupled with PE was correlated with a good outcome in case 2, while the levels of IL-6 remained elevated regardless of CHDF coupled with PE because case 3 remained febrile with superinfections. However, CHDF coupled with PE might lessen the aggressive clinical course and prolong survival.

The pathophysiology of STSS offers a highly complicated scenario. In STSS, Spes induce a complex and dynamic cellular response, giving rise to several mediators known to be

relevant in the pathogenesis of septic shock such as specific mediators, substances responsible for up- or down-regulation of cytokine receptors and cytokine antagonists, inactivators of translational or transductional pathways, and precursor molecules. Prompt modulation of the inflammatory cascade have led to improved outcomes and to improve hemodynamics in STSS. It seems of great importance to explore all possible treatment techniques that may have a direct impact on circulating mediators of STSS and may interfere also with the imbalance between proinflammatory and anti-inflammatory substances in critically ill patients with STSS. Once an optimal adsorptive substrate has been identified in STSS, the application of CHDF coupled with hemoperfusion and PE appears to open the door to effective therapeutic options. The search for innovative treatments specifically targeted to the cytokines of critically ill patients with STSS seems therefore more important than the attempt to adjust concepts and technologies that are normally applied to patients with endotoxic shock.

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