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BRIEF REPORT

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Septic shock after liver transplantation for Caroli's disease: clinical improvement after treatment with C1-esterase inhibitor

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Abstract The extent of complement and contact activation is related to outcome in sepsis. A low functional index of their main blocker C1-esterase inhibitor (C1-INH) is considered as a relative deficiency of C1-INH and might contribute to the development of fatal complications in the intensive care unit. The first results of therapeutic intervention with C1-INH concentrate in septic shock are promising. We report on our experience of C1-INH concentrate administration in a young woman with Caroli's disease as ultimate rescue therapy for septic shock with capillary leakage syndrome after combined liver and kidney transplantation. No focus of infection was detectable and thus surgical intervention was not indicated. Antibiotic therapy at that time included vancomycin, tobramycin, meropenem and fluconazol. Hemodynamic stabilization occurred within hours after administration of C1-INH concentrate. Simultaneously a reduction in vasopressor medication was possible and negative fluid balance was achieved.

Key words C1-esterase inhibitor · Complement system · Sepsis · Liver transplantation · Caroli's disease · Colloid osmotic pressure

Introduction

Severe sepsis is currently the leading cause of death in surgical intensive care units (ICUs) with a mortality of over 50%. When illness deteriorates to septic shock, massive volume substitution, inotropic agents and vasopressors are needed to maintain adequate circulation. Due to increased vasopermeability and vasodilation, shock frequently remains refractory and edema develops with a gain in body weight. In this clinical situation, overwhelming complement and contact activation are present and the extent of their stimulation is considered to be related to outcome [1]. Both systems are regulated by C1-esterase inhibitor (C1-INH) and its increased consumption in septic shock has been demonstrated [2]. A low functional index indicates a relative deficiency of C1-INH and has been suggested to contribute to a destructive inflammatory response and fatal complications [2]. This new pathophysiologic approach and the high mortality of the underlying diseases resulted in the first therapeutic attempts with C1-INH. Preliminary results are encouraging [1, 3].

Caroli's disease is an uncommon congenital disorder of the intrahepatic biliary tree with dilatation of the

bile ducts. The clinical course is often complicated by recurrent episodes of bacterial cholangitis. Despite use of a broad spectrum antimicrobial agents, medical treatment is frequently unsuccessful due to the persistence of bacteria in dilated bile ducts. Other therapies, including internal or external biliary drainage and various surgical or endoscopic procedures, have often proved to be ineffective [4]. Despite surgical treatment, sepsis remains a typical complication with poor results of antimicrobial therapy.

In diffuse forms of Caroli's disease, liver resection is seldom feasible because of associated congenital hepatic fibrosis. In this setting, liver transplantation is reported as an effective form of treatment [5–7].

We present a patient with Caroli's disease after combined liver and kidney transplantation who had a prolonged postoperative course due to infectious complications. During a period of septic shock, where no surgical or other medical treatment option remained, we decided to treat the patient with C1-INH concentrate as ultimate rescue therapy.

Case report

A 24-year-old woman was admitted to ICU after combined liver and kidney transplantation for Caroli's disease after a history of numerous septic periods and polycystic renal disease. Previously, the patient had rejected two kidney transplants. Because the main infectious focus had been the bileduct, this time combined liver and kidney transplantation was performed. After initial stabilization, the patient developed acute necrotizing pancreatitis on the second postoperative day. Daily surgical intervention including lavage of abdomen apertum and necrectomy had to be performed. On postoperative day 10, she developed an infectious thrombosis of the graft artery and received a second liver transplant. Additionally, a tracheotomy was performed. After retransplantation, acute renal failure occurred and the patient required continuous venovenous hemofiltration. Therapy for acute necrotizing pancreatitis with open lavage had to be continued for 2 weeks and was further complicated by abdominal infection (*Klebsiella oxytoca*, *Escherichia coli*). Five weeks postoperatively, a kidney transplant biopsy revealed acute rejection which led to a change in immunotherapy to FK 506 and steroids instead of cyclosporin and steroids. Eight weeks postoperatively, the patient developed sepsis due to *Enterococcus faecium* and *E. coli*, which was successfully treated with vancomycin, levofloxacin and tobramycin. After 10 weeks, mild acute liver graft rejection was diagnosed by liver biopsy, which responded well to methylprednisolone pulse therapy. Thereafter the patient underwent a weaning process.

Three months postoperatively, the patient developed septic symptoms and required augmented mechanical ventilation again. Computed tomography (CT) showed the development of an abscess surrounding the transplanted kidney and this led to nephrectomy. Intraoperative surface biopsy revealed *E. faecium* (sensitive to vancomycin) and *E. coli*. In subsequent days several surgical interventions were necessary for bleeding and lavage at the surgical site (left iliac fossa).

Then, 106 days after admission to the ICU infection parameters increased again with hemodynamic and respiratory instability. Blood cultures were negative. Abdomen, chest and paranasal sinuses were re-examined by CT but no infectious focus was detectable. Endocarditis was excluded by echocardiography. Despite these results, the clinical situation worsened: the patient required controlled mechanical ventilation and the hemodynamics deteriorated in spite of adequate volume resuscitation and norepinephrine administration. Clinically, the patient showed increasing edema. Since antibiotic therapy already included vancomycin, meropenem, tobramycin and fluconazol, no other option for intervention remained.

In this situation of refractory septic shock, C1-INH functional levels were found to be in the normal range. Thus it was decided to administer C1-INH concentrate (Berinert HS, Centeon, Liederbach, Germany) as ultimate rescue therapy. The patient received 60 U/kg body weight as bolus over 1 h followed by continuous administration of 30 U/kg per 24 h for 4 days (1 U is the amount in 1 ml normal plasma and is equivalent to 2.5 μmol/l). No side effects attributable to C1–INH were observed. Functional and antigenic C1-INH levels were determined using chromogenic substrate assay Berichrom C1-Inaktivator (Behringwerke, Marburg, Germany) and single radial immunodiffusion assay NOR-Partigen (Behringwerke, Marburg, Germany) [8]. The normal range for both methods is 70–130%. Both functional and antigenic levels of C1–INH increased. Stabilization of hemodynamic parameters with a simultaneous reduction in norepinephrine dosage occurred within hours (Table 1). Negative fluid balance with stabilized central venous pressure was achieved during the next few days by continuous venovenous hemofiltration (Fig. 1). Parallel colloid osmotic pressure was increased and the edema diminished. Respiratory function improved and mechanical ventilation was switched to an augmented mode 5 days after C1-INH was started (Table 1). Three months later, the patient was discharged from the ICU without any evidence of infection. Rehabilitation is now being carried out.

Discussion

To our knowledge, this is the first report on a patient after combined liver and kidney transplantation in Caroli's disease with capillary leakage syndrome (CLS) and septic shock, who has been successfully treated with administration of C1–INH concentrate.

Bacterial cholangitis is the most frequent and life-threatening complication of Caroli's disease. Due to the persistence of gram-negative bacilli in the dilated bile ducts, medical treatment is difficult and improvement usually temporary and achieved only with continuous parenteral antibiotic administration.

Kidney transplantation had to be performed because of polycystic renal disease when the patient was 11 years old. Sufficient levels of immunosuppression were in conflict with several chologenic-septic periods despite broad spectrum antibiotic therapy, as is typical for Caroli's disease. Because the patient had already lost two kidney transplants, the decision for a combined liver and kidney transplant was taken to eliminate the liver as an infectious focus. Whereas in all published cases the postoperative course has been uncomplicated, in our patient infectious problems persisted. During one septic period, the patient developed septic shock. This time no surgical or medical intervention remained.

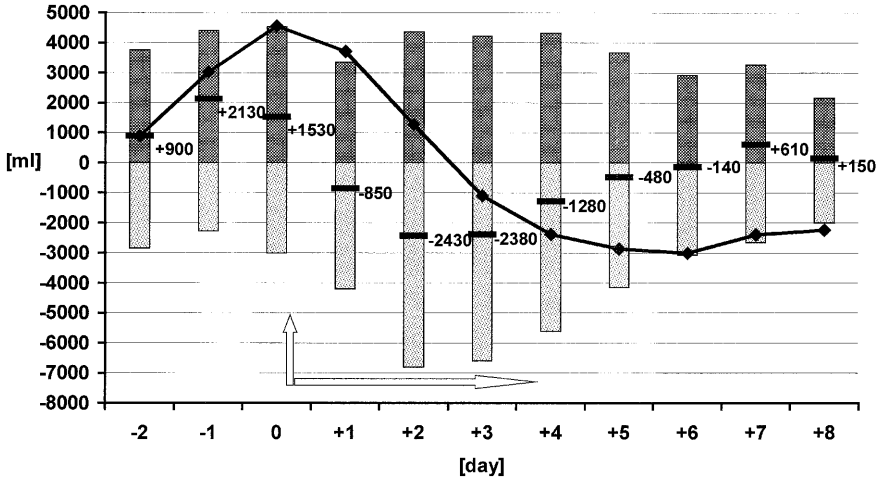

Fig. 1 Cumulative and daily fluid balance before, during and after C1-INH administration (*fluid input* ▦ *fluid output* ▨), *daily fluid balance* — (numbers show quantity in ml) and *cumulative balance* from 2 days before C1-INH therapy –◆–; C1-INH administration: *bolus* ⇑ and *continuous injection* ⇒

Table 1 Hemodynamics, respiratory function and functional and antigenic levels of C1-INH after treatment with C1-INH concentrate (*MAP* mean arterial pressure, *CVP* central venous pressure, *COP* colloid osmotic pressure, PaO_2/FIO_2 arterial oxygen tension/fractional inspired oxygen ratio)

	Time							
	Before	+6 h	+24 h	+2 days	+3 days	+4 days	+5 days	+6 days
C1-INH activity (%)	125	152	161	167	140	149	132	116
C1-INH quantity (%)	169	199	218	238	232	259	245	206
Norepinephrine (μg/kg per min)	0.15	0.15	0.06	0.06	0.06	0.075	0.075	0.04
MAP (mm Hg)	67	100	117	95	105	137	92	83
CVP (mm Hg)	12	17	16	9	8	10	12	12
COP (mm Hg)	20	22	20	22	25	24	21	22
PaO_2/FIO_2 (mm Hg)	303	407	500	460	473	507	487	470

Since a relative deficiency of C1-INH is associated with the development of septic shock and CLS, it was decided to measure levels of C1-INH in this patient. Despite it being an acute phase protein, functional levels of C1-INH were in the normal range, indicating the proposed relative deficiency. Thus, C1-INH concentrate was given as ultimate rescue therapy.

For many years acute attacks of hereditary angioedema have been treated by intravenous administration of C1-INH without any serious side effects. Thus, it was assumed that high doses of C1-INH might also be beneficial for patients with septic shock. The first results with C1-INH substitution in CLS induced by interleukin IL-2 therapy [1] or following bone marrow transplantation [3] are promising. These results suggest a role of complement in the pathogenesis of CLS. In a study which has been presented in part high antigenic levels of C1-INH measured in septic shock patients were significantly higher in nonsurvivors, while functional levels remained within the normal range in spite of being an acute phase protein in both survivors and nonsurvivors. This was interpreted as a relative deficiency of C1-INH in septic shock [9]. In a second study [10] on patients in septic shock, C1-INH concentrate was substituted in a regimen according to Hack et al. [1]. We could not confirm their results of increasing functional levels, whereas antigenic levels were significantly increased. Since an increased turnover of C1-INH leading to a low functional index in septic shock due to complex formation and cleavage has been reported, we interpret our data as a rapid consumption of administered C1-INH. After substitution, antigenic levels of C1-INH were found to be decreasing on the 3rd day, which was the rationale for the modified dosage regimen in the case presented.

A few hours after administration of C1-INH concentrate, there was rapid stabilization of the circulation. Our patient needed less vasopressor medication, edema diminished, negative fluid balance was achieved and colloid osmotic pressure increased. Within 3 days, the fluid balance was normalized. This may indicate an improvement of CLS. Levels of antigenic and functional C1-INH was increased. This indicates that substitution of C1-INH is able to adjust its relative deficiency in septic shock. Apparently, as suggested by other authors, substituted C1-INH may react partially with its target proteases or may be cleaved, for example by neutrophile elastase [2].

In conclusion, hemodynamic stabilization with simultaneous reduction of vasopressor therapy and normalization of fluid balance occurred in the patient after administration of C1-INH concentrate. Double-blind, controlled studies are warranted to confirm these encouraging results of C1-INH therapy in patients suffering from septic shock and CLS.

References

1. Hack CE, Ogilvie AC, Eisele B, Eerenberg AJ, Wagstaff J, Thijs LG (1993) C1-inhibitor substitution therapy in septic shock and in the vascular leak syndrome induced by high doses of interleukin-2. Intensive Care Med 19 [Suppl] 1:S19–S28
2. Nuijens J, Eerenberg-Belmer A, Huijbregts C, Schreuder W, Felt-Bersma R, Abbink J, Thijs L, Hack C (1989) Proteolytic inactivation of plasma C1-inhibitor in sepsis. J Clin Invest 84: 443–450
3. Nurnberger W, Heying H, Burdach S, Göbel U (1997) C1 esterase inhibitor concentrate for capillary leakage syndrome following bone marrow transplantation. Ann Hematol 75: 95–101
4. Landen S, Bardaxoglou E, Maddern GJ, Delugeau V, Gosselin M, Launois B (1993) Caroli's disease: a surgical dilemma. Acta Chir Belg 93: 224–226
5. Sans M, Rimola A, Navasa M, Grande L, Garcia Valdecasas JC, Andreu H, Salmeron JM, Mas A, Rodes J (1997) Liver transplantation in patients with Caroli's disease and recurrent cholangitis. Transpl Int 10: 241–244
6. Schiano TD, Fiel MI, Miller CM, Bodenheimer HC Jr, Min AD (1997) Adult presentation of Caroli's syndrome treated with orthotopic liver transplantation. Am J Gastroenterol 92: 1938–1940
7. Balsells J, Margarit C, Murio E, Lazaro JL, Charco R, Vidal MT, Bonnin J (1993) Adenocarcinoma in Caroli's disease treated by liver transplantation. HPB Surg 7: 81–86
8. Bork K, Kolde H (1986) Angioneurotisches Ödem und andere C1-Inaktivator-Funktionsstörungen: Neue funktionelle Bestimmungsmethode. Diagnose und Labor 36 (8):8–15
9. Vangerow B, Marx G, Leuwer M, Rueckoldt H (1997) C1-Inhibitor-Aktivität, Flüssigkeitsbilanz und 30-Tage Mortalität bei septischen Patienten. Intensivmed 34 [Suppl 1]:49
10. Vangerow B, Marx G, Leuwer M, Rueckoldt H (1998) C1-Inhibitor substitution as ultima ratio therapy in septic shock: experience with 15 patients. Crit Care Med 2 [Suppl 1]:19