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*Case Report*

# A Case of Refractory Systemic Capillary Leak Syndrome (Clarkson's Disease) during Pregnancy

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**A 32-year-old woman, pregnant with twins, presented with a chief complaint of general fatigue. Her general condition had rapidly deteriorated since her last visit to the primary obstetrician; the patient was then referred to our hospital because of suspected fetal death. She underwent emergency cesarean section because fetal death had indeed occurred, and she was then admitted to the intensive care unit (ICU). On ICU admission, she was found to be in shock. Laboratory analysis revealed extreme hemoconcentration and a low albumin level, and initially, septic shock with obstetric complications was suspected. However, because she did not respond to conventional therapy but instead, rapidly developed severe generalized edema, systemic capillary leak syndrome (SCLS) was diagnosed. The patient remained in shock for several days until undergoing plasma exchange (PE), despite some earlier empirical treatments. She eventually recovered from profound shock status and was discharged from the ICU without sequelae. Among potentially effective treatments, PE seemed to be the most reasonable choice for the treatment of her SCLS.**

**Key words:** systemic capillary leak syndrome, plasma exchange, pregnancy

Systemic capillary leak syndrome (SCLS) is a rare but life-threatening disorder first described by Clarkson et al. in 1960[1]. There have been several reports on SCLS and potentially effective treatments including fluid resuscitation [1–12], continuous renal replacement therapy [4,6], low-dose corticosteroid treatment [1,2,4,8,12], continuous inotrope infusion [1,3,6–8,11,12], high-dose intravenous immunoglobulin (IVIG) therapy [9,11], pulse corticosteroid treatments [4–6], and plasma exchange (PE) treatments [10]. Although the etiology of SCLS is still unclear, many reports have suggested that some kind of autoimmune pathway is implicated in the pathology of this disease [9,13]. Of those treatments, steroids, IVIG therapy, and PE have the potential to induce resolution through immunomodulation.

Here we report the case of a patient with SCLS alongside therapy-refractory shock after an emergency cesarean section, who recovered after the initiation of PE. Consent for publication was obtained directly from the patient.

## Case Report

The patient was a 32-year-old woman pregnant with twins. She had been previously healthy and had one healthy daughter. She had no problems with the current pregnancy until gestational week 27. Her chief complaint then was general fatigue, and she was

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referred to our hospital by her primary obstetrician because of suspected fetal death. Admission laboratory data revealed extreme hemoconcentration (hemoglobin 20.3 g/dL, hematocrit 58.3%), low serum albumin (2.2 g/dL), high lactate (5.5 mmol/L), and compensated metabolic acidosis. Because the twin fetuses had indeed already died *in utero*, an emergency cesarean section was performed. During surgery, the obstetrician observed a mass-like region on her descending colon and called a general surgeon, who suggested observational follow-up. The cesarean section was completed, and the patient was then admitted to the intensive care unit (ICU). Although the procedure was successful, her postsurgical condition rapidly deteriorated. Initially, septic shock accompanied by obstetrical complications was suspected, and therapy consisted of antibiotics (meropenem and clindamycin on day 1, meropenem and arbekacin on days 2–10), fluid, and vasopressors. Continuous renal replacement therapy was then initiated because of acute kidney injury. Laboratory data on admission to our hospital and within the first 10 days in the ICU are shown in Table 1.

Because the therapies administered had little effect on the patient's clinical condition, low-dose hydrocortisone was administered for 3 days. Despite this, on ICU day 3, the patient began to complain of dyspnea due to a large persistent pleural effusion that resulted in intubation (Fig. 1). The patient was sedated using fentanyl, dexmedetomidine, and midazolam. Her white blood cell count remained high, her hemoglobin remained concentrated, and her albumin level stayed low despite 12.5–50 g of albumin administration for the first 7 days. The rapidly progressing generalized edema (Fig. 1), persistent hemoconcentration, and shock status, despite the substantial fluid administration, led to the diagnosis of SCLS. To identify an increase in monoclonal paraproteins, we submitted a blood sample to immune electrophoresis on ICU day 4, which turned out to be negative 3 days later. Even

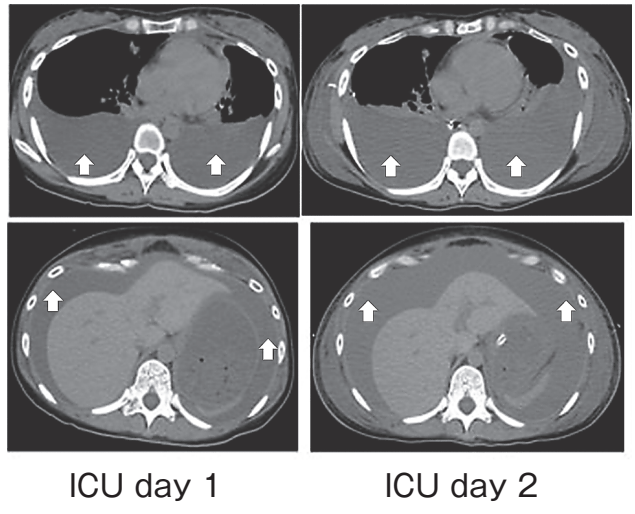


**Fig. 1** Chest and abdominal computed tomography confirmed rapid progressive bilateral pleural effusions and ascites. White arrows indicate bilateral pleural effusions (upper figures) and an ascites (lower figures).

**Table 1** Laboratory data of first 10 days in the ICU

| | ICU day | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| WBC (/μL) | 42,700 | 59,100 | 65,600 | 45,700 | 32,100 | 42,600 | 45,000 | 42,700 | 30,600 | 29,400 | 19,400 |
| Hct (%) | 58.3 | 43.5 | 36.1 | 36.3 | 23.3 | 32.2 | 29.1 | 38.3 | 31.8 | 35.9 | 28.9 |
| Alb (g/dL) | 2.2 | 2.1 | 1.2 | 1.7 | 1.9 | 1.2 | 0.7 | 0.6 | 1.3 | 1.9 | 1.7 |
| PCT (ng/mL) | | 11.4 | 18.2 | 16.6 | 20.3 | 11.6 | | | 6.9 | 6.7 | 5.7 |
| CRP (mg/dL) | 22.8 | 11.8 | 9.5 | 7.4 | 4.8 | 3.5 | 2.2 | 2.8 | 3.8 | 6.5 | 6.2 |
| hCG (mIU/mL) | | | | 397 | | | | | 73.8 | | |
| β-hCG (mIU/mL) | | | | 387 | | | | | 82.8 | | |
| Estradiol (pg/mL) | | 419 | | 400 | | | | | 252 | | |
| CEA (ng/mL) | | | 1.47 | | | 1.42 | | | | | |
| CA19-9 (U/mL) | | | 2.4 | | | 11.9 | | | | | |
| CA125 (U/mL) | | | 13.3 | | | | | | | | |
| Immune electrophoresis | | | | | No bands | | | | | | |

ICU, intensive care unit; WBC, white blood cell; Hct, hematocrit; Alb, albumin; PCT, procalcitonin; CRP, C-reactive protein; hCG, human chorionic gonadotropin; CEA, carcinoembryonic antigen; CA, cancer antigen.
ICU day 0 represents the data on admission.

after the diagnosis was made, we still suspected sepsis and obstetrical complications. Obstetrical complications were considered highly unlikely due to the serum estradiol and $\beta$-human chorionic gonadotropin levels, which were within normal post-delivery limits (Table 1). The descending colon mass was also evaluated using computed tomography (CT) and tumor markers. On CT, the mass looked like an invagination, and the serum carcinoembryonic antigen, cancer antigen 19–9, and cancer antigen 125 levels were 1.47 ng/mL, 2.4 U/mL, and 13.3 U/mL, respectively; these were all within normal ranges. Exploratory surgery was considered, but ruled out due to the patient' poor physical status.

On ICU day 3, a continuous epinephrine infusion at 0.05 $\mu$g/kg/min was started, but without any beneficial effect. IVIG (1 g/kg/day for 3 days; Venoglobulin 5% IV; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was also initiated. In addition, pulse steroid therapy (methylprednisolone 10 mg/kg/day for 3 days) was initiated following the low-dose corticosteroid therapy. However, these therapies did not seem to affect her status; the total amount of fluid administration exceeded 10,000 mL/day. On ICU day 5, although we had not obtained the immune electrophoresis results, we decided to perform PE due to the severity and persistence of her condition. PE was performed with 3,000 mL of fresh frozen plasma exchanged during 100-min procedures 3 days in a row. The amount of fluid administered on the first PE day was markedly reduced, and her body weight, which had been increasing, began to plateau. On ICU day 6, while undergoing the second PE, her blood pressure considerably increased to a mean arterial pressure of $>65$ mmHg. After the second PE, her pulse pressure widened, blood pressure stabilized, and shock status subsided. The ICU course for the first 10 days is shown in Fig. 2.

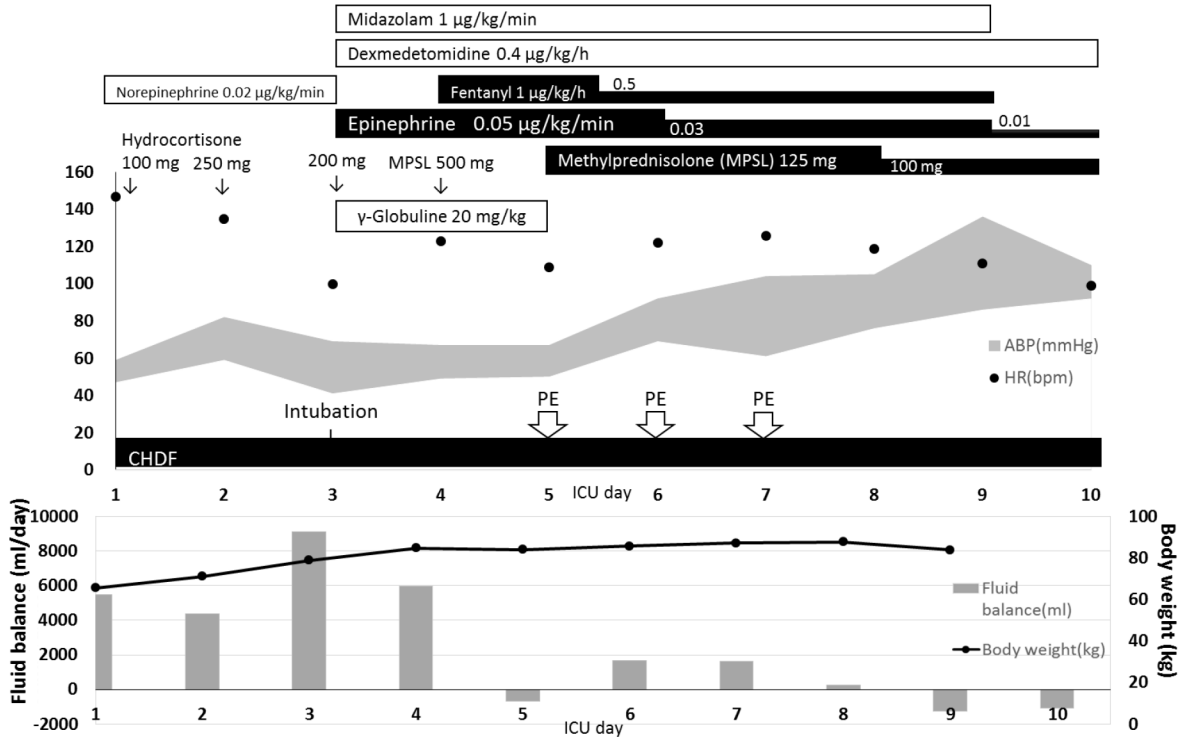


Fig. 2 The patient course for the first 10 days in the intensive care unit (ICU) is shown in the upper panel. The wide white downward arrows indicate when PE was performed. On ICU day 6, during the second PE, her mean blood pressure increased to $>65$ mmHg and her pulse pressure widened. The lower two panels show fluid in–out balance and body weight. ABP, arterial blood pressure; HR, heart rate; MPSL, methylprednisolone.

After she recovered from the profound shock, her status became more stable daily, although it took substantial time to reduce her body weight. However, on ICU day 22, fecal matter was discharged through the abdominal drain that had been placed in the surgical wound on ICU day 5 for preventing abdominal compartment syndrome. The reason for the panperitonitis became apparent when a tumor-like mass, detected on the first CT scan and during the surgery, was found to be a ruptured adenocarcinoma. An emergency Hartmann procedure was performed. Although a tracheostomy was required for long-term respirator management on ICU day 29, the remainder of the ICU course was unremarkable. She made the transition from hemodiafiltration to hemodialysis on ICU day 44 and was eventually withdrawn from hemodialysis on ICU day 52. The tracheostomy was closed on ICU day 62, and she was discharged from the ICU on day 67. She has been undergoing chemotherapy for descending colon cancer since her ICU discharge and remains otherwise healthy at the time of this writing.

## Discussion

SCLS is a rare syndrome first reported by Clarkson *et al.* [1]. Its etiology remains uncertain and its diagnosis is sometimes difficult. In the present case, the salient points for diagnosis were hemoconcentration and rapidly progressing generalized edema [1–14]. Increase in monoclonal paraproteins has been observed in approximately 76–89% of SCLS patients [3,13,14]. However, no reports have confirmed that monoclonal gammopathy was a pathogenic factor. In this case, we performed immune electrophoresis, but bands were absent.

The differential diagnosis included paraneoplastic syndrome associated with colon cancer, sepsis, and ovarian hyperstimulation syndrome. Ovarian hyperstimulation syndrome was ruled out based on the patient's serum estradiol level. Sepsis was not completely ruled out, but we had never experienced sepsis with such dense hemoconcentration and severe generalized edema. There have been 2 previous case reports of SCLS associated with cancer [15,16], and indeed, paraneoplastic syndrome could not be completely ruled out as a pathogenic factor of SCLS in our patient.

In this case, the patient exhibited markedly high white blood cell counts consisting mostly of neutrophils. There have been reports showing an association between high serum granulocyte colony-stimulating factor (G-CSF) levels and SCLS [17–19]; in addition, G-CSF is highly expressed in human colon cancer [20]. Although the serum G-CSF level was not measured in our patient, she may have had a high serum G-CSF level that caused leukocytosis. A reduction of G-CSF after PE might have contributed to the improvement of our patient's status. Several previous reports focused on the prophylaxis of repetitive shock episodes [10–14], but few have reported the details of therapeutic steps taken to relieve the critical, profound shock. PE seems to be a rare therapeutic choice for reversing shock in SCLS. There are almost no reports of its use for this indication during the past decade. Kapoor *et al.* [10] reported one case treated with PE, but the report was lacking in details. PE is believed to exert its immunomodulatory effect by eliminating soluble proteins, including molecules as large as 1,000–3,000 kDa [10].

Recently, several reports have described the therapeutic efficacy of high-dose immunoglobulin administration for the profound hypovolemic shock of SCLS [9,12]. The mechanisms by which IVIG exerts preventive effects against hypervascular permeability are not fully understood, but the effect is suggested to be immunomodulation, mainly owing to the production of cytokines and cytokine antagonists [22]. Lambert *et al.* [9] reported that IVIG of 1 g/kg/day markedly reversed SCLS within 48 h. We administered the same amount of immunoglobulins (1 g/kg/day or 50 g/day) for 3 days without any remarkable effect. Because, in SCLS, molecules as large as 900 kDa can leak through the vasculature [2], it is possible that the administered IVIG also leaks into the extravascular spaces and thus cannot exert beneficial effects.

In conclusion we report a patient with SCLS refractory to empirical therapies who immediately recovered after the commencement of PE therapy. In light of the cost and safety, PE should not be performed too readily; however, it may be considered when a patient is experiencing profound therapy-refractory shock, even though SCLS is generally considered to be a self-limited disease.

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