CASE REPORT

Chronic systemic capillary leak syndrome associated with an intravascular large B-cell lymphoma in a patient undergoing hemodialysis: a case report with literature review

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Abstract

Background: Systemic capillary leak syndrome (SCLS) is a rare disorder characterized by hypotension, hemoconcentration, and hypoalbuminemia associated with increased capillary endothelium permeability. Patients with a chronic form of SCLS present with persistent and progressive generalized edema. However, there have been no reports of chronic SCLS in patients undergoing hemodialysis. Herein, we report a case of chronic SCLS associated with an intravascular large B-cell lymphoma (IVLBCl) in a patient undergoing hemodialysis.

Case presentation: An 71-year-old male had been on hemodialysis for five years due to diabetic nephropathy. Difficulty in body fluid removal was observed during hemodialysis, and the patient was admitted to our hospital due to exacerbated weight gain and lower limb edema. He had elevated serum lactate dehydrogenase (LDH) levels and thrombocytopenia. His blood pressure was low, and his serum brain natriuretic peptide level was relatively low, despite the increase in body fluid volume. His clinical characteristics suggested a chronic form of SCLS. Random skin biopsy revealed IVLBCL; however, the association between IVLBCL and chronic SCLS remained unclear. He underwent chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone, followed by rituximab. After the treatment, his serum LDH level decreased, and the difficulty in body fluid removal during hemodialysis improved. The patient's chronic SCLS seemed to be complicated by IVLBCL.

Conclusions: Patients with chronic SCLS who are undergoing hemodialysis seem to present with difficulties in fluid removal. The frequency of SCLS complications in cases with malignant lymphomas, including IVLBCL, is considered to be extremely low. However, clinicians should be aware of SCLS as a complication of malignant lymphomas.

Keywords: Hemodialysis, Systemic capillary leak syndrome, Intravascular large B-cell lymphoma

Background

Systemic capillary leak syndrome (SCLS) is a rare disorder that is characterized by hypotension, hemoconcentration, and hypoalbuminemia, and is associated with increased permeability of the capillary endothelium to proteins [1–3]. The classical acute form of SCLS presents
with rapid onset of hypovolemic shock and systemic edema due to plasma leakage. After several days, the permeability of the endothelium spontaneously improves and the patient’s blood pressure recovers [2]. In contrast, patients with chronic forms of SCLS present with persistent and progressive generalized edema without signs of recovery [4, 5]. However, there have been no reports of chronic SCLS in patients undergoing hemodialysis.

SCLS can be idiopathic; however, it can also be caused by other diseases, or by drugs [3]. Although malignancies can lead to SCLS [6], there have been few reports of SCLS associated with an intravascular large B-cell lymphoma (IVLBCL). Herein, we report a case of a patient who experienced difficulty in body fluid removal during hemodialysis, which seemed to be a symptom of chronic SCLS associated with IVLBCL.

Case presentation
A 71-year-old male had been undergoing hemodialysis for 4 years due to diabetic nephropathy. He had a medical history of end-stage renal disease due to hypertension and type 2 diabetes. His serum lactate dehydrogenase (LDH) level has been gradually increasing since February 20xx, and his platelet count gradually decreased from June 20xx. However, he exhibited no other symptoms, including loss of appetite and hypotension. From early August 20xx, he developed loss of appetite and his blood pressure began to decline on both dialysis and non-dialysis days. From August 14, it became difficult to remove fluid during hemodialysis and he subsequently gained body weight. In the same period, his serum albumin level dropped to less than 3 mg/dL in the absence of anuria or diarrhea. No drugs were added during this period. He was admitted to our hospital on August 25, 20xx due to exacerbated weight gain and lower limb edema. His body weight at admission was 60.9 kg, which had increased by more than 6 kg from his dry weight (DW) in early August. The patient’s blood pressure was 80/53 mmHg, and his body temperature was 36.5 °C. Thoracoabdominal pelvic computed tomography showed right pleural effusion, a small amount of ascites, and subcutaneous edema, although no other abnormalities were observed. Echocardiography showed no decrease in contractility. Laboratory examination revealed serum total protein and serum albumin levels of 4.2 g/dL and 2.0 g/dL, respectively. The patient’s hemoglobin and hematocrit were 11.0 g/dL and 33.0%, respectively, which were within the normal ranges for patients undergoing hemodialysis. The white blood cell count was 2600/mm³, and the platelet count was 30,000/mm³. The levels of serum LDH, soluble interleukin-2 receptor (sIL-2R), C-reactive protein, and ferritin were 2444 U/L (normal range: 119–229 U/L), 3140 U/mL (normal range: 121–613 U/mL), 1.15 mg/dL (normal level: <0.3 mg/dL), and 194.5 ng/mL (normal range: 16.4–323 ng/mL), respectively. Monoclonal gammopathy was not observed. The serum brain natriuretic peptide (BNP) level remained slightly high at 36.0 pg/mL (normal level: <18.4 pg/mL) despite the increase in body fluid volume, suggesting extravasation of fluid. We suspected hematologic malignancy, including IVLBCL, due to his extremely high serum LDH level and thrombocytopenia. We hence performed a bone marrow biopsy and random skin biopsy. The bone marrow biopsy showed 20–30% cellularity with a decrease in megakaryocytes.
and mild hemophagocytosis (Fig. 1). No atypical cells were observed in the bone marrow. The random skin biopsy revealed atypical large cells with prominent nucleoli in the blood vessels of the dermis up to the subcutaneous fat; these cells were CD20 positive as per immunohistochemical analysis (Fig. 2). The histopathological findings were consistent with a diagnosis of IVLBCL; however, the patient’s clinical manifestations suggested unclear associations between the chronic form of SCLS and IVLBCL. Based on the diagnosis of IVLBCL, the patient underwent chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) 9 days after admission, and rituximab 14 days after admission. After chemotherapy, the serum LDH level gradually decreased, blood pressure increased, and the difficulty in fluid removal during hemodialysis improved. The patient’s edema was ameliorated by reducing the DW; however, there was no clear change in the amount of pleural effusion and ascites on imaging studies. Despite improvement in serum LDH levels, blood pressure, and fluid removal, the patient experienced a loss of appetite and his general condition worsened. Although the second cycle of CHOP and rituximab was administered 51 and 52 days after admission, respectively, the patient experienced disturbance of consciousness and it once again became difficult to remove fluid during hemodialysis. Moreover, he developed a fever, despite receiving antibiotics. Exacerbation of IVLBCL was considered; however, we believed that he would not tolerate additional examination and treatment based on his general condition, and the patient died 84 days after admission. The patient’s clinical course before and after admission is shown in Fig. 3.

Discussion and conclusions
We encountered a case of difficulty in body fluid removal during hemodialysis that was considered to be a symptom of a chronic form of SCLS. The patient’s chronic SCLS also seemed to be associated with IVLBCL, because treatment for IVLBCL appeared to lead to improvement in the patient’s symptoms.

In 1960, Clarkson et al. described a woman with progressively declining blood pressure; edema in the face, arms, and legs; and rising hematocrit levels. The unexplained shock and anasarca were quickly managed through massive diuresis after several days [1]. Similar to our experience, the classical acute form of idiopathic SCLS presents with rapid shock, anasarca, hemoconcentration, and hypoalbuminemia due to unexplained extravasation of protein-rich fluid [2]. Shock, anasarca, and hemoconcentration can cause multiorgan dysfunction, including acute kidney injury, rhabdomyolysis, pleural and pericardial effusions, and thrombosis [2, 3]. After a variable number of days, fluids are mobilized from the interstitial space to the intravascular space, followed by recovery of blood pressure and diuresis. Patients with idiopathic SCLS experience this series of events repeatedly; however, their frequency and severity vary among patients [2]. Although the definite mechanism of idiopathic SCLS is unknown, it has been reported that some proinflammatory mediators (C-X-C motif chemokine ligand 10, C–C motif chemokine ligand 2, and interleukin-6) and angiogenic permeability factors, including vascular endothelial growth

Fig. 2 Pathology of intravascular large B-cell lymphoma. A Skin biopsy reveals atypical large lymphoid cells in the blood vessels of the dermis up to the subcutaneous fat (arrowheads, hematoxylin and eosin staining). B The atypical large cells are noted to be immunoreactive for CD20
factor and angiopoietin-2, are elevated in the acute sera of patients with SCLS [7, 8]. Additionally, monoclonal gammopathy is present in more than 50% of patients with idiopathic SCLS; nevertheless, its importance in the pathogenesis of the disease is unclear [2, 3].

SCLS can be caused by other potential factors that are associated with increased capillary endothelial permeability. Although sepsis is the most common cause of this phenomenon, other diseases or drugs can also cause SCLS [3]. Malignancies are reportedly associated with SCLS. Shin et al. reviewed 62 case reports of SCLS associated with cancer or cancer-related drugs [6] and found that SCLS was associated with cancer in 27 cases; with anti-cancer agents, such as granulocyte-colony stimulating factor and interleukin-2 in 32 cases; and with bone marrow transplantation in 3 cases. Among the 27 cases of SCLS associated with cancer, 16 were of hematologic malignancies, including diffuse large B-cell lymphoma [6]. In a report of non-Hodgkin’s lymphoma complicated with anasarca, the patients had elevated tumor necrosis factor alpha (TNF-α) levels, which could be one of the causes of capillary endothelial hyperpermeability [9].

There are only a few case reports on the chronic form of SCLS [4, 10–15]. Unlike the classical form, patients with chronic SCLS experience mild progressive generalized edema, along with pleural and pericardial effusions without signs of spontaneous recovery. Idiopathic chronic SCLS reportedly shows a therapeutic response to systemic steroids [10, 15] or to intravenous immunoglobulin [12]. Moreover, chronic SCLS induced by gemcitabine has also been reported [13, 14]. Although there are no reports on SCLS in patients undergoing hemodialysis, Alkhunaizi et al. described a case of idiopathic chronic SCLS in a patient who did not respond to several therapeutic agents and who developed acute kidney injury that required hemodialysis [11]. This patient had massive edema despite daily hemodialysis, which was suggestive of difficulty in body fluid removal during hemodialysis. In our case, after the elevation of serum LDH and thrombocytopenia, the patient had difficulty in fluid removal during hemodialysis. In our case, after the elevation of serum LDH and thrombocytopenia, the patient had difficulty in fluid removal during hemodialysis and progressive edema, pleural effusions, and weight gain. He had hypotension, hypoalbuminemia, and a relatively low serum BNP level despite a weight gain of ≥ 6 kg, which were suggestive of extravasation of fluid. This clinical characteristic was suggestive of

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**Fig. 3** Clinical course before and after admission. Before admission, the serum lactate dehydrogenase (LDH) level increased, systolic blood pressure (sBP) declined, and body weight after hemodialysis (HD) increased due to difficulty in fluid removal. After the first cycle of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), in addition to rituximab (RTX), the serum LDH level and body weight decreased, and the blood pressure increased after fluid removal was improved. The second cycle of CHOP and RTX was administered; however, the patient experienced disturbance of consciousness and fever, and it once again became difficult to remove fluid during hemodialysis. The patient died 84 days after admission.
chronic SCLS, which could lead to difficulty in body fluid removal during hemodialysis. In our patient, chronic SCLS seemed to have been caused by IVLBCL.

IVLBCL is a rare form of diffuse large B-cell lymphoma that is characterized by the growth of tumor cells within the lumen of small- to intermediate-sized blood vessels. According to the World Health Organization classification in 2017, IVLBCL is classified into three types based on their clinical characteristics, namely the classic variant, the cutaneous variant, and the hemophagocytic syndrome-associated variant [16]. Patients with the classical variant present with fever of unknown origin as a nonspecific systemic symptom, and with various organ-related manifestations in the skin, central nervous system, endocrine organs, and lungs. The cutaneous variant is common in Western countries, with most symptoms localized to the skin and only a few being systemic. The hemophagocytic syndrome-associated variant is most common in Asian countries, characterized by bone marrow involvement, hepatosplenomegalgy, and thrombocytopenia, which are not observed in other variants. This variant shows rapid progression and has a poor prognosis. Laboratory abnormalities are common in each variant, with high serum LDH and high sIL-2R levels [17–19]. In a report of 25 patients with the hemophagocytic syndrome-associated variant, fever, hepatomegalgy, and/or splenomegalgy were present in all patients, anemia and/or thrombocytopenia were present in 22 patients, and tumor cells were detected in the bone marrow of 19 patients. Serum interleukin-6 levels were elevated in all patients that were examined, while the serum TNF-α and interferon-gamma levels were only elevated in some; however, none of the patients presented with symptoms suggestive of SCLS [20]. Regarding the treatment of IVLBCL, the addition of rituximab to the CHOP regimen is recommended [19].

Our patient had hemophagocytosis in the bone marrow as well as thrombocytopenia, which is consistent with the hemophagocytic syndrome-associated variant of IVLBCL. However, it is considered atypical that he had no fever or hepatosplenomegaly. Moreover, no tumor cells were found in his bone marrow, but the random skin biopsy revealed IVLBCL. It has been reported that random skin biopsy is a reliable method for the diagnosis of IVLBCL when patients have symptoms, such as fever of unknown origin, elevated serum LDH level, thrombocytopenia, hypoxemia, and alteration of consciousness [21, 22]. Our patient had an extremely high serum LDH level and thrombocytopenia, which were suspected to be because of IVLBCL, and tumor cells were confirmed on random skin biopsy. We were unable to examine inflammatory cytokines; therefore, we could not investigate the pathophysiology of chronic SCLS in this patient. Nevertheless, the chronic SCLS in this case seemed to have been caused by IVLBCL, because after treatment with rituximab and CHOP chemotherapy, the patient’s serum LDH level decreased, blood pressure simultaneously increased, and the difficulty in body fluid removal during hemodialysis improved. We believe that we could not adjust the DW to the actual weight lost due to the patient’s loss of appetite is the reason why the amount of pleural effusion and ascites did not change.

The frequency of SCLS complications in patients with malignant lymphomas, including IVLBCL, is considered to be extremely low; however, some cases may be under-recognized. In our case, difficulty in removing fluid during hemodialysis, which was associated with chronic SCLS, was an important symptom. Therefore, clinicians should suspect SCLS if patients receiving hemodialysis have unexplained difficulties in fluid removal, and be aware that malignant lymphomas may be one of the causes of SCLS.

**Literature review**

There are several reports of IVLBCL presenting with anasarca, and some cases may have been associated with SCLS [23–27]. A summary of cases, including ours, is shown in Table 1. All cases presented with progressive edema as the initial symptom, and fever, which is a frequent feature of IVLBCL, was not observed. In three cases, a decrease in blood pressure was observed [23–25], which may have been due to extravasation of fluid. In a case of acute kidney injury that required hemodialysis, the patient had low central venous pressure despite having anasarca [26]. Serum LDH levels were elevated in all cases described except one. Two patients were diagnosed with IVLBCL on autopsy [23, 24]. Interestingly, all other cases including ours case were diagnosed using skin biopsy [25–27]. In one case, chemotherapy could not be commenced because of unstable hemodynamics [25]. In the remaining two cases, the patients received CHOP chemotherapy and rituximab, and the anasarca improved as IVLBCL was cured [26, 27]. As above, patients with IVLBCL rarely seem to develop progressive edema without other symptoms. These cases are difficult to diagnosis; however, random skin biopsy may be useful in making the right diagnosis if malignant lymphoma is suspected in a patient with elevated serum LDH levels. It is important to diagnose IVLBCL early and to treat it in order to avoid disease progression.

The pathophysiology of IVLBCL causing anasarca has not been adequately investigated in these cases. In our case, the patient had difficulty in fluid removal during hemodialysis as the initial feature, and this was suggestive of extravasation of fluid. Our case indicates that
extravasation of fluid as seen in chronic SCLS relates to the mechanism of IVLBCL causing generalized edema.

Abbreviations
BNP: Brain natriuretic peptide; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisolone; DW: Dry weight; IVLBCL: Intravascular large B-cell lymphoma; LDH: Lactate dehydrogenase; SCLS: Systemic capillary leak syndrome; sIL-2R: Soluble interleukin-2 receptor; TNF-α: Tumor necrosis factor alpha.

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Authors’ contributions
KS, RS, KY, and AO took care of the patient. KS, RS, HN, TK, and SI decided the treatment. KS drafted the manuscript and is responsible for the manuscript. TK and SI helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Declarations
Ethics approval and consent to participate
This case report was approved by the Ethical Committee of Tosei General Hospital and was in compliance with the Declaration of Helsinki.

Consent for publication
Written informed consent was obtained from the family of the patient for publication of this case report and accompanying images.

Competing interests
The authors declare that they have no competing interests.

Table 1  Clinical features of intravascular large B-cell lymphoma presenting generalized edema

| Case | Age (years)/sex | Clinical symptoms | Blood test data | Diagnosed method | Treatment | Outcome |
|------|-----------------|-------------------|-----------------|------------------|-----------|---------|
|      |                 | Hypotension Fever | Albumin (g/dL) | LDH (U/L)        |           |         |
| [23] | 69/male         | +                 | 2.2             | 600              | Autopsy   | Died    |
| [24] | 74/female       | +                 | N.D             | 707              | Autopsy   | Died    |
| [25] | 82/male         | +                 | 1.6             | 1891             | Skin biopsy | Not performed due to unstable hemodynamics | Died |
| [26] | 56/female       | N.D               | 3.46            | N.D              | Skin biopsy | Rituximab and CHOP | Alive |
| [27] | 64/male         | N.D               | N.D             | 4577             | Skin biopsy | Rituximab and CHOP | Alive |
| Our case | 71/male      | +                 | 2.0             | 2444             | Skin biopsy | Rituximab and CHOP | Died |

CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; LDH: lactate dehydrogenase; N.D: not documented.

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