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A case of chronic systemic capillary leak syndrome (SCLS) exacerbated during SARS-CoV2 infection

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Abstract. – Systemic capillary leak syndrome (SCLS) is a very rare and lethal disease characterized by hemoconcentration and hypoalbuminemia caused by reversible plasma extravasation. The underlying cause for SCLS remains largely unknown and acute treatment has remained mainly supportive. Prophylaxis with intravenous immunoglobulin (IVIG) has been shown to successfully prevent further episodes in affected patients. We reported a case of SCLS in a patient who presented to our hospital with COVID-19 and developed profound shock.

Key Words:
Systemic capillary leak syndrome, COVID-19, SARS-CoV2, Shock, Capillary permeability.

Introduction

Systemic capillary leak syndrome (SCLS) is a rare and life-threatening disorder, first described by Clarkson et al[1] in 1960. They reported a case of a 32-year-old woman who suffered an abrupt remarkable loss of plasma which caused edema and hypovolemic shock. SCLS is characterized by recurrent episodes of unexplained hypotension, hemoconcentration, and hypoalbuminemia as a consequence of leakage of plasma and proteins to the extravascular space. SCLS can be caused by cancer, drugs, infections or surgery[2], but can as well occur as idiopathic SCLS after secondary causes are ruled out. Up to 90% of patients carry a monoclonal gammopathy of undetermined significance (MGUS), mostly IgG. However, in a few patients SCLS recurs episodically in the absence of an identified cause. Moreover, the chronic form of SCLS is extremely rare, with only a few cases reported in the literature[3-7]. The pathogenesis is poorly understood and is believed to be a manifestation of transient endothelial dysfunction due to endothelial contraction, apoptosis, injury, or a combination of these factors[8]. The causes of SCLS are known and several theories of pathogenesis have been proposed: (a) increased hydrostatic pressure within capillaries can release fluid and proteins through the endothelial barrier and into interstitium; (b) decreased capillary oncotic pressure may fail to retain fluid within the vascular space; (c) increased capillary permeability (fluid and proteins pass through the endothelial barrier and into interstitium too readily) secondary to sepsis, anaphylaxis and certain infectious diseases[9-11]. Recently, Case et al[12] reported a patient with SCLS associated with Coronavirus disease 2019 (COVID-19) infection. We reported another case of SCLS in a patient who presented to our hospital with COVID-19 pneumonia and developed profound shock.

Case Report

A 58-year-old man with a past medical history of systemic arterial hypertension and SCLS (with only one exacerbation in 2008 because of influenza A virus infection) presented to our Internal Medicine COVID Unit with symptoms of fever, diarrhea, nausea, and arterial hypotension for two days. The antigenic nasopharyngeal swab test was positive for SARS-CoV2 at admission. He disclosed to have been 7 days earlier in close contact with his brother-in-law suffering from COVID-19.

The physical examination revealed a body temperature of 37.2°C, blood pressure of 90/60 mm Hg, pulse of 110 beats per minute, respiratory rate of 14 breaths per minute, and oxygen saturation of 98% while the patient was breathing ambient air. Lung auscultation revealed rhonchi,

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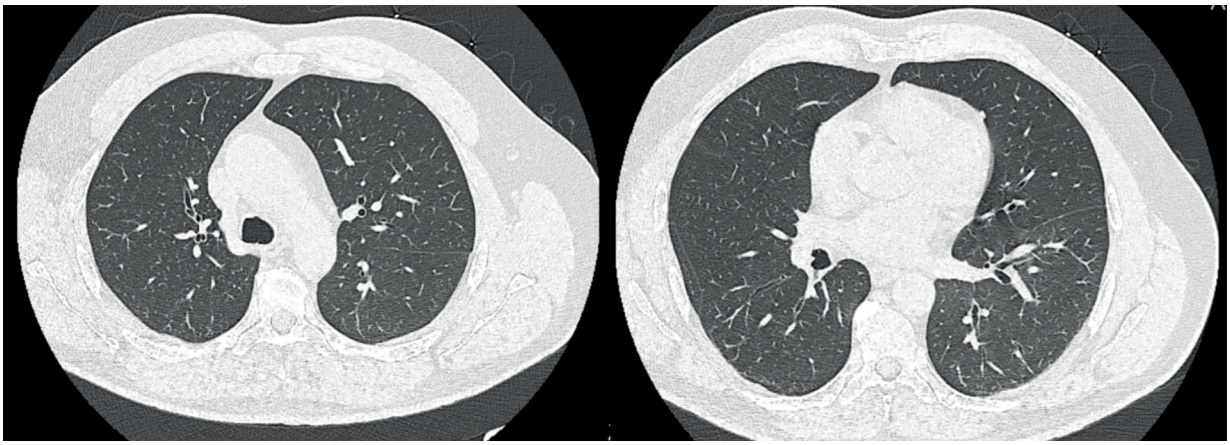

Figure 1. Chest Computed Tomography (Illness Day 3, Hospital Day 1). Axial nonenhanced chest CT image shows absence of ground-glass opacities.

and chest CT scan showed no parenchymal abnormalities (Figure 1). His antihypertensive therapy (olmesartan/amlodipine 40/5 mg) was discontinued. Laboratory results on hospital admission reflected elevated levels of creatinine (1.3 mg/dL), hemoglobin (17.3 g/dL), C reactive protein (1.02 mg/dL) and d-dimer 1444 mcg/L. (Table I). After admission, the patient received supportive care, including 1 liter of normal saline and ondansetron for nausea.

The patient's vital signs got worse during the first day of hospitalization, in particular the patient showed severe hypotension (blood pressure of 60/40 mmHg) unresponsive to volume crystalloid resuscitation. Subsequent blood tests showed hemoconcentration, hypoalbuminemia, creatinine elevation and lactic acidosis of 4.3 mmol/L. Analytical blood results before, during, and after the initial presentation are summarized in Table I. Electrocardiogram (ECG) and echocardiography were normal. Given the changing clinical presentation and concern about his past medical history with a previous SCLS diagnosis, treatment with human immunoglobulin IgG (IVIG) (a 2 g/kg dose for 80 kg) administered intravenously was initiated, based on previous reports of its efficacy in acute SCLS[13]. Albumin supplementation and vasopressor therapy with noradrenaline was performed. The patient was subsequently transferred to the intensive care unit (ICU) for intensive monitoring and to continue therapy with inotropes. His vasopressor requirements were norepinephrine at 0.5 mg/kg/min. Because of his hypotension and elevated white blood cell count, a diagnosis of afebrile sepsis was suspected, and he was treated empirically with antibiotics. During the ICU recovery (after blood pressure normalization and plasma volume improvement), the patient developed persistent dry cough and oxygen saturation values decrease up to 90% at FiO2 of 21%. On the sixth day of hospitalization, the patient was started on oxygen treatment with nasal cannula at 2 liters per minute. A chest CT scan performed on the same day showed evidence of bilateral interstitial pneumonia of the lower lobes and posterior segments of the upper lobes (Figure 2). Urinary antigen testing for Streptococcus pneumoniae and Legionella pneumophila, Chlamydia and Mycoplasma serology and nasopharyngeal swab for Influenza A and B virus were all negative. Urine and blood cultures were also negative. The patient was treated with remdesivir (a 200 mg loading dose followed by 100 mg administered intravenously every day for 5 days in total), enoxaparin 6000 UI subcutaneously and dexamethasone 6 mg intravenously. On hospital day 7 noninvasive ventilation (NIV) with continuous positive airway pressure (CPAP) Helmet (PEEP 12.5 mmHg, FiO2 100%) was started due to the rapid worsening of respiratory exchanges. On hospital day 9 the patient was supported with high flow nasal cannula. He continued supplemental oxygen in our Unit with a decrease in oxygen flows until hospital day 20 without other complications. After oxygen discontinuation, the patient was afebrile, with all symptoms resolved except for his cough, which was decreasing in severity. On hospital day 22 the patient was discharged with the indication to follow the antihypertensive therapy previously taken and to perform monthly intravenous infusion of immunoglobulins at a dosage of 1 g/kg.

Table I. Clinical Laboratory Results.

Measure	Reference range	Hospital day 1 (h 03:00 a.m.)	Hospital day 1 (h 11:00 p.m.)	Hospital day 2	Hospital day 3	Hospital day 5	Hospital day 8	Hospital day 13	Hospital day 18
Vhite-cell count (per µl)	4000-10000	9680	17700	23280	16300	4440	3370	5010	5910
Red-cell count (per µl)	4.200.000 - 5.700.000	6.060.000	7.470.000	6.990.000	5.350.000	3.860.000	3.260.000	4.600.000	4.310.000
Absolute neutrophil count (per µl)	1900-7400	6290	14710	19670	14410	3810	2410	3710	3710
Absolute lymphocyte count (per µl)	1000-3900	2070	1660	2070	950	380	500	850	1630
Platelet count (per µl)	150.000 - 400.000	324.000	366.000	360.000	279.000	115.000	180.000	257.000	202.000
Hemoglobin (g/dl)	13.2-17	17.3	21.7	20.1	15.3	11	12.2	12.8	12.6
Hematocrit (%)	39-50	50	61.9	59	45	32.6	36.5	39.1	37.1
Sodium (mmol/liter)	136-145	139	136	140	133	135	137	138	139
Potassium (mmol/liter)	3.5-5.1	4.01	4.63	5.32	4.5	4.0	4.1	4.5	4
Chloride (mmol/liter)	98-107	110	111	107	102	105	106	106	103
Calcium (mg/dl)	8.7-10.4	7.3	7.9	7.6	8.34	7.98	8.1	8.2	9.1
Glucose (mg/dl)	65-140	123	147	132	122	84	103	97	90
Blood urea nitrogen (mg/dl)	9-23	19	28	43	32	21.56	20	18	17
Creatinine (mg/dl)	0.7-1.3	1.3	2.4	3.4	2.86	0.92	0.75	0.68	0.79
Total protein (g/dl)	5.7-8.2	7.1	6.8	6.4	8.3	6.9	7.1	7.2	8
Albumin (g/dl)	3.2-4.8	3	2.6	2.7	2.3	2.8	2.7	2.6	3
Total bilirubin (mg/dl)	0.3-1.2	0.28	0.21	0.26	0.42	0.38	0.4	0.42	0.39
Procalcitonin (ng/ml)	<0.05	0.3	0.56	0.94	0.48	0.3	0.23	0.04	0.02
Alanine aminotransferase (U/liter)	10-49	26	22	24	20	50	30	30	22
Aspartate aminotransferase (U/liter)	<33	21	14	14	10	37	23	20	39
C reactive protein (mg/dl)	<0.5	1.02	1.14	0.9	2.3	7.5	7.2	1.8	0.2
Ferritin (ng/ml)	30-400	129	132	125	326	442	439	386	51
Fibrinogen (mg/dl)	150-450	361	305	265	350	382	470	421	243
D-dimer (mcg/liter)	<550	1444	1004	1068	1079	1201	1150	1129	850
Lactate dehydrogenase (U/liter)	120-246	133	181	153	159	201	258	221	125
International normalized ratio	0.9-1.1	1.21	1.37	1.23	1.1	1.11	1.01	1.1	0.98
Creatine kinase (U/liter)	62-325	144	179	226	166	77	156	66	17
Venous lactate (mmol/liter)	0.4-2.0	2.2	4.3	3.2	1.7	0.8	0.9	0.8	0.8

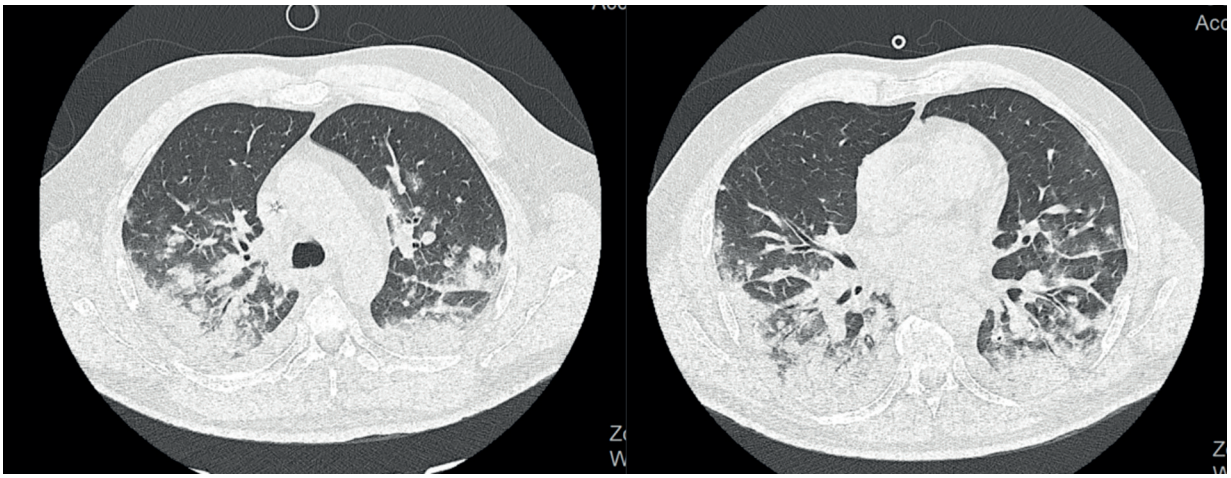

Figure 2. Chest Computed Tomography (CT) (Illness Day 8, Hospital Day 6. Axial nonenhanced chest CT image shows the appearance of bilateral ground-glass opacities.

The patient has provided informed consent for this report.

Discussion

SCLS is characterized by episodic arterial hypotension, edema, hemoconcentration, and hypoalbuminemia, due to extravasation of fluid and proteins from the intracellular space into the interstitial space. The recurrence of episodes is variable between patients[8]. SCLS is a diagnosis of exclusion and is easily misidentified with anaphylaxis, sepsis, or angioedema[14]. The pathogenesis of SCLS is not well understood and the site of vascular endothelial increased permeability is still unknown[1,8]. The triggers for acute episodes of SCLS are not yet identified with certainty, however viral infections, sepsis, anaphylaxis, or intense physical exertion frequently preceded SCLS, suggesting a role for inflammation in acute SCLS[11]. Studies[14,15] have shown the elevation of multiple cytokines such as CXCL10 (C-X-C motif chemokine ligand 10), angiopoietin-2 and vascular endothelial growth factor in acute SCLS serum compared with control. The appropriate disease-specific treatment of SCLS is currently unknown. Successful abortive therapy with intravenous immunoglobulins has been described[13]. We reported the first SCLS exacerbation thirteen years after the first and only episode in a 58-year-old man with SARS-CoV2 infection. We also illustrated several aspects of this rare disease that are not yet fully understood. Our case patient had an acute SCLS recurrence triggered by SARS-CoV2 infection, and his hospital recovery was complicated with severe hypotension, hemoconcentration, hypoalbuminemia, acute kidney injury (AKI) and respiratory failure secondary to COVID-19 interstitial pneumonia. The first case of the onset of SCLS secondary to COVID-19 infection was described in 2020. Case et al[12] described a patient with acute COVID-19 infection who presented with hemoconcentration, shock and hypoalbuminemia. To our knowledge, our case is the first report of a recurrence of acute episode of SCLS due to Coronavirus 2019 infection in a patient with chronic SCLS who had presented the first acute manifestation in 2008 following influenza A virus infection. The occurrence of acute SCLS after a viral infection allows to speculate on virus involvement in the capillary alteration.

A typical feature of SARS-CoV-2 is that the virus does not only infect airway epithelial cells, but also endothelial cells[16]. It is unclear whether the replication in endothelial cells in COVID-19 occurs in all infected patients or only in certain groups. COVID-19 has a worse outcome in patients with arterial hypertension, diabetes, and cardiovascular disease, all comorbidities associated with endothelial dysfunction[17]. Furthermore, clinical signs in severe COVID-19 are consistent with vascular function impairment e.g., thrombosis, angiopathies and multi-organ endothelial damage[18].

SARS-CoV-2's ability to infect endothelial cells is shared by many emerging viruses with

great relevance to human health. Indeed, endothelial injury was confirmed also in infection caused by other viral pathogens, such as Nipah and Hendra henipavirus, Hantavirus, Influenza A, H5N1, H7N1, Ebolavirus, Dengue virus, Zikavirus and West Nile virus[19]. The endothelium's ability to serve as a barrier between the intravascular and interstitial spaces depends on the integrity of binding between neighboring endothelial cells[20]. The maintenance of microvascular integrity relies on crosstalk between two key components of the endothelium: the glycocalyx and the intercellular junctions. There are two types of cell junctions that form the barrier: adherens junctions (AJ) and tight junctions. The major component of the AJ is represented by vascular endothelial cadherin. Mild inflammatory stimuli cause vascular endothelial cadherin internalization, which weakens the AJ and increases permeability without losing integrity of the endothelial architecture. Severe inflammatory stimuli cause endothelial cell separation, resulting in significant increases in permeability[21,22]. Xie et al[15] showed that serum from patients experiencing an acute SCLS episode induces endothelial permeability through remodeling of endothelial cell-cell junctions. SARS-CoV2 is an endotheliotropic virus that causes direct extensive endothelial damage and endotheliitis with severe vascular impairment, edema, microvascular thrombosis, and bleeding. We here reported the rare case of SCLS exacerbated during SARS-CoV2 infection. According to current evidence regarding SCLS and SARS-CoV2 in endothelial cells impairment, it can be assumed a possible bi-directional pathophysiological link between these two conditions. Moreover, the action of SARS-CoV2 on endothelium could induce alterations of the capillaries resulting in the onset of pathophysiological cascade of SCLS. However, it is notable that in our case the patient developed clinical signs of acute SCLS in the early stage of SARS-CoV2 infection, before the pulmonary involvement, indicating a possible direct role of the virus in the genesis of capillary barrier damage.

Conclusions

Although shock has been described at the clinical beginning of COVID-19 due to diarrhea, dehydration, poor oral intake, we report a case of a patient with chronic SCLS that could have been exacerbated during SARS-CoV2 infection. Despite it being an anecdotal case, our report suggests a direct role of SARS-CoV2 infection in the onset of barrier endothelial alteration typical of SCLS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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