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Systemic Capillary Leak Syndrome Secondary to COVID-19 Infection: Case Report

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Abstract

Introduction: Systemic capillary leak syndrome (SCLS) is an increasingly recognized rare syndrome. Its diagnosis is suggested by the occurrence of edema with arterial hypotension, hemoconcentration, and paradoxical hypoalbuminemia. SCLS can be idiopathic (Clarkson syndrome) or secondary. Secondary SCLS (SSCLS) is mainly triggered by infections (especially viruses), drugs (antitumor therapy), malignancies, and inflammatory diseases. We report a case of systemic capillary leak syndrome secondary to the COVID-19 infection. **Observation:** A 74-year-old chronic smoker with no particular history was initially admitted to the intensive care unit (ICU) with a picture of respiratory distress secondary to a COVID-19 infection with favorable evolution, hence his transfer to the emergency services. On Day 8 of hospitalization, following the installation of arterial hypotension, not responding to filling, associated with hypoalbuminemia, and generalized edematous syndrome, and in the absence of any other explanation for this clinical picture, a SCLS secondary to COVID-19 infection was suggested. On the balance sheet, after the discovery of acute renal failure, serum creatinine went from 7.9 mg/l to 16.6 mg/l with microalbuminuria at 420 mg/24h and leukocyturia at 20 elements/mm^3 without germ-evoked tubulointerstitial nephritis (TIN) secondary to a viral infection with COVID-19. The evolution was marked by the spontaneous regression of the edema and the normalization of the blood pressure figures. **Discussion:** The classic triad combining hypotension, hemoconcentration, and hypoalbuminemia suggests the diagnosis of SCLS once all other causes of shock have been ruled out. Hemoconcentration is less constant in SSCLS than in ISCLS. This is the case with our patient. The exact pathophysiological process of SCLS is largely unknown. Viral infections are the

most common infectious cause of SCLS. The kidneys are the second-most common organs affected by the SARS-Cov-2 coronavirus infection. The presence of nephritis can be used as an indicator of SCLS, which can be a predictor of serious complications such as fluid overload, respiratory failure, and the need for ICU admission. **Conclusion:** In the event of COVID-19 infection, the appearance of hypotension and hypoalbuminemia with the gradual onset of generalized edema should suggest SCLS. The establishment of close monitoring is mandatory, given the risk of fatal evolution. Fortunately, for our patient, the evolution was favorable.

Keywords

Hemoconcentration, Low Blood Pressure, COVID-19, Tubulointerstitial Nephritis

1. Introduction

Capillary hyperpermeability syndrome, or SCLS, is a rare syndrome characterized clinically by generalized edema and arterial hypotension, which can go as far as a state of shock, and biologically by the almost pathognomonic association of hemoconcentration, and paradoxical hypoalbuminemia. SCLS is caused by a greatly increased permeability of the capillary walls of blood vessels, which leads to massive leakage of plasma into the interstitium.

SCFS can be idiopathic (Clarkson syndrome) or secondary. SSCFS is mainly triggered by infections (especially viruses), drugs (antitumor therapy), malignant tumors, and inflammatory diseases. We report a case of SCLS secondary to the COVID-19 infection.

2. Observation

A 74-year-old man, a chronic smoker, was admitted to intensive care for respiratory distress following a COVID-19 infection. 4 days before admission, the patient presented with a fever of 39.5, chills, a dry cough, and progressively worsening dyspnea. On chest CT, viral pneumonitis lesions compatible with COVID-19 infection, with an estimated percentage of damage of 75%, were classified as CORAD-5. The COVID-19 PCR was positive. The examination on admission to the intensive care unit found a conscious patient, GCS 15/15, normotensive at 120/72 mmHg, tachycardic at 100 bpm, warm extremities, Polypneic at 40 cycles/min, SpO_2 at 80% on ambient air, substernal and intercostal in drawing without cyanosis. The SpO_2 was 96% under NIV and 40 % under FiO_2.

The biological assessment on admission found normal renal function, with serum creatinine at 7.9 mg/l. C-reactive protein was elevated at 123 mg/l, hyperferritinemia at 667 ng/ml, and the LDH level was elevated at 388 U/L. A high level of fibrinogen at 5 g/l and D-Dimer at 0.32 µg/ml.

Therapeutically, the patient was put on methylprednisolone at a dosage of 160

mg/day intravenously, anticoagulation based on low molecular weight heparin (LMWH) at a dosage of 6000 IU/24 hours, and bi-antibiotic therapy for the lungs combining (Amoxicillin/Clavulanic acid) at a dosage of 1 g/8h and ciprofloxacin at a dosage of 500 mg/24h. The clinical and biological evolution was favorable.

A few days later, the patient presented with arterial hypotension at 94/61 mmHg, not responding to filling, hence the introduction of vasoactive drugs, with tachycardia at 120 beats/min, without fever or signs of infection at the clinical examination.

The evolution was marked by the persistence of hypotension under low doses of norepinephrine and the progressive installation of a generalized edematous syndrome. In addition, the diuresis was preserved and quantified at 2.5 liters/24 h.

Hypoalbuminemia at 22 g/l had set in as well as renal failure, with creatinine going from 7.9 mg/l to 16.6 mg/l. The urinary assessment found microalbuminuria at 420 mg/24h and non-nephrotic proteinuria at 0.7 g/24h, without hematuria, with aseptic leukocyturia at 20 elements/mm3. In the presence of micro-albuminuria and leukocyturia, tubulointerstitial nephritis was evoked. Transthoracic ultrasound showed a left ventricular ejection fraction of 61% and a low abundance of pericardial effusion; BNP was normal at 68 pg/ml. Liver function tests were normal and showed no cytolysis or cholestasis: AST was 34 IU/L, ALT was 51 IU/L, PAL was 112 IU/L, GGT was 62 IU/L, and Factor V was 140% normal.

In the presence of hypotension and the context of COVID-19 infection, the first diagnosis that was mentioned was septic shock, which was eliminated given the absence of positive infectious markers and individualized germ. Heart failure was also mentioned, in the presence of the edematous syndrome, but a transthoracic ultrasound without abnormality and a normal BNP level, this diagnosis was eliminated.

Various causes for edematous syndrome, hypotension, and hypoalbuminemia were considered, but all were ruled out. Given the absence of other etiologies that could explain the shock, the systemic leak syndrome was retained. And since SCLS appeared during the COVID-19 infection and no other triggers were identified, SCLS secondary to the COVID-19 infection was suspected.

For the treatment of his SCLS, the patient received only liquid resuscitation with recourse to physiological solutions. The hemodynamic state of the patient eventually improved, with regression of the edemas and normalization of the biological assessments. (**Table 1**)

3. Discussion

SCLS is a rare, life-threatening disorder characterized by transitory and recurrent episodes of vascular endothelial hyperpermeability [1].

To date, less than 500 cases have been reported. SSCLS can be difficult to diagnose because its manifestations are often preceded by flu-like prodromes and

Table 1. Results of laboratory analyzes carried out over 5 days after the onset of CLS.

Results of laboratory analyzes		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Hemoglobin	**N: [12- 15] (g/dl)**	8	8.3	8.5	9.2	9.5	9.1
Hematocrit	**N: [36 - 44] (%)**	38.8	40.0	36.7	28.1	26.4	24
Leukocytes	**N: [4 -11] (10^3/µl)**	9.03	7.65	7.61	7.52	8.19	7.43
Neutrophils	**N: [2.5 -7] (10^3/µl)**	7.37	5.44	5.10	4.02	4.3	5.21
Lymphocytes	**N: [1- 4.8] (10^3/µl)**	0.73	1.25	1.45	2.47	2.82	1.08
Platelets	**N: [150 - 450] (10^3/µl)**	192	233	336	412	400	402
Prothrombin time	**N: [70 - 100] (%)**	81	NR	NR	NR	NR	NR
Albumin	**N: [34 - 54] (g/l)**	19	22	23	25	28	34
Creatinine	**N: [7 - 13] (mg/l)**	14.3	16.6	16.6	16.6	14.5	10
D-dimers	**N < 0.5 µg/ml**	0.55	NR		0.36		0.32
Proteinuria	**N < 0.3 g/24h**	0.44	0.46	0.46	0.3	0.26	NR
ASAT	**N: [8 - 48] (UI/L)**	34	NR	NR	NR	NR	NR
ALAT	**N: [7 - 55] (UI/L)**	51	NR	NR	NR	NR	NR
GGT	**N: [5 - 40] (UI/L)**	62	NR	NR	NR	NR	NR
PAL	**N: [44 - 147] (UI/L)**	112	NR	NR	NR	NR	NR
FV	**N: [50 - 150] (%)**	140	NR	NR	NR	NR	NR
BNP	**N < 125 pg/ml**	68	NR	NR	NR	NR	NR
Troponin	**N < 0.04 ng/ml**	0.005	NR	NR	NR	NR	NR
Cortisol	**N: [10 - 20] µg/dl**	13.4	NR	NR	NR	NR	NR
TSH	**N: [0.4 - 4] (µUI/ml)**	0.65	NR	NR	NR	NR	NR
T3	**N: [2 - 6] (pg/ml)**	2.2	NR	NR	NR	NR	NR
T4	**N: [6.7 - 20] (ng/l)**	8.1	NR	NR	NR	NR	NR

Abbreviations: N: Normal, NR, unrealized.

can be mistaken for sepsis. However, there are no perfectly defined criteria for SFCS, and pathologies whose presentation may be similar should be eliminated (Table 2).

Once all other causes of shock have been ruled out, the classic triad combining hypotension, hemoconcentration, and hypoalbuminemia supports the diagnosis of SCLS [2]. Literature data suggest that hemoconcentration is less constant during SFCS than during ISCLS. Moreover, in our patient with SSCLS, the hemoconcentration was not found, which is in line with the results already published.

The exact pathophysiological process of SSCLS is largely unknown. Several pathophysiological hypotheses have been considered, such as an inflammation-mediated mechanism or an alteration of the capillary endothelium. An exacerbation is usually caused by a viral upper respiratory tract infection [3] [4]. The COVID-19 infection was mentioned first in our patient.

The main causes of SSCLS are certain infections, especially viral ones, hematological malignancies, and medications (Table 3).

Viral infections are the most common infectious causes of SSCLS, the foremost among which are viral hemorrhagic fevers [5] [6]. They are the cause of both SSCLS by endothelial dysfunction and consumption thrombocytopenia within the framework of disseminated intravascular coagulation. A case of recurrent SSCLS at one year has been described concomitantly with infection by the influenza A virus (proven by rapid diagnostic tests) [7], but the occurrence of a relapse suggests that it could in fact be a case of ISCLS. A case of SCLS was described following the management of hypovolemic shock secondary to Rotavirus diarrhea in an 8-month-old infant [8]. Three days after massive rehydration, generalized edema associated with hypoalbuminemia and high hematocrit

Table 2. Differential diagnoses of edematous or hypotensive episodes [3].

Nephrotic syndrome
Heart failure
Acute adrenal insufficiency
Mastocytosis
Hypothyroidism
Angioedema
Protein-losing enteropathy

Table 3. Etiology of secondary capillary leak syndromes [3].

Infections
Viral: viral hemorrhagic fever, influenza, Epstein Barr Virus
Bacterial: Chlamydia pneumonia, brucellosis, sepsis
Blood diseases and their complications
Lymphoproliferative syndromes
Acquired macrophage activation syndrome
Graft versus host disease
Drugs and poisons
IL2
G-CSF and GM-CSF
Anti-cancer chemotherapy (vinorelbine, bortezomib, cyclosporine, etc.)
Carbon monoxide poisoning
Postoperative and post-traumatic
Surgery under extracorporeal circulation
Operated necrotizing enterocolitis
Dermatological and systemic pathologies
Psoriasis
Cutaneous T-cell lymphoma
Kawasaki disease

appeared. Finally, a case of EBV infection has been reported associated with SFCS [9]. Several publications indicate that the new SARS-CoV-2 coronavirus does not only affect the lungs but also many other organs, such as the kidneys, which are the second most frequently affected.

Along the same lines, a May 2020 publication from the German University Hospital Göttingen recommends admission to the ICU for tubulointerstitial nephritis (TIN) in patients with COVID-19. The presence of TIN can be used as an indicator of systemic capillary leak syndrome (SCLS), which can be a predictor of serious complications such as fluid overload, respiratory failure, and the need for ICU admission.

Thus, an algorithm was proposed for the early detection of nephritis associated with COVID-19 (**Figure 1**).

Patients with no or only one nephritis criterion and/or serum albumin concentrations greater than 25 g/l were at low risk of decompensation and ICU admission. For these patients, it was recommended to reassess patients daily and repeat urine tests every 3 days.

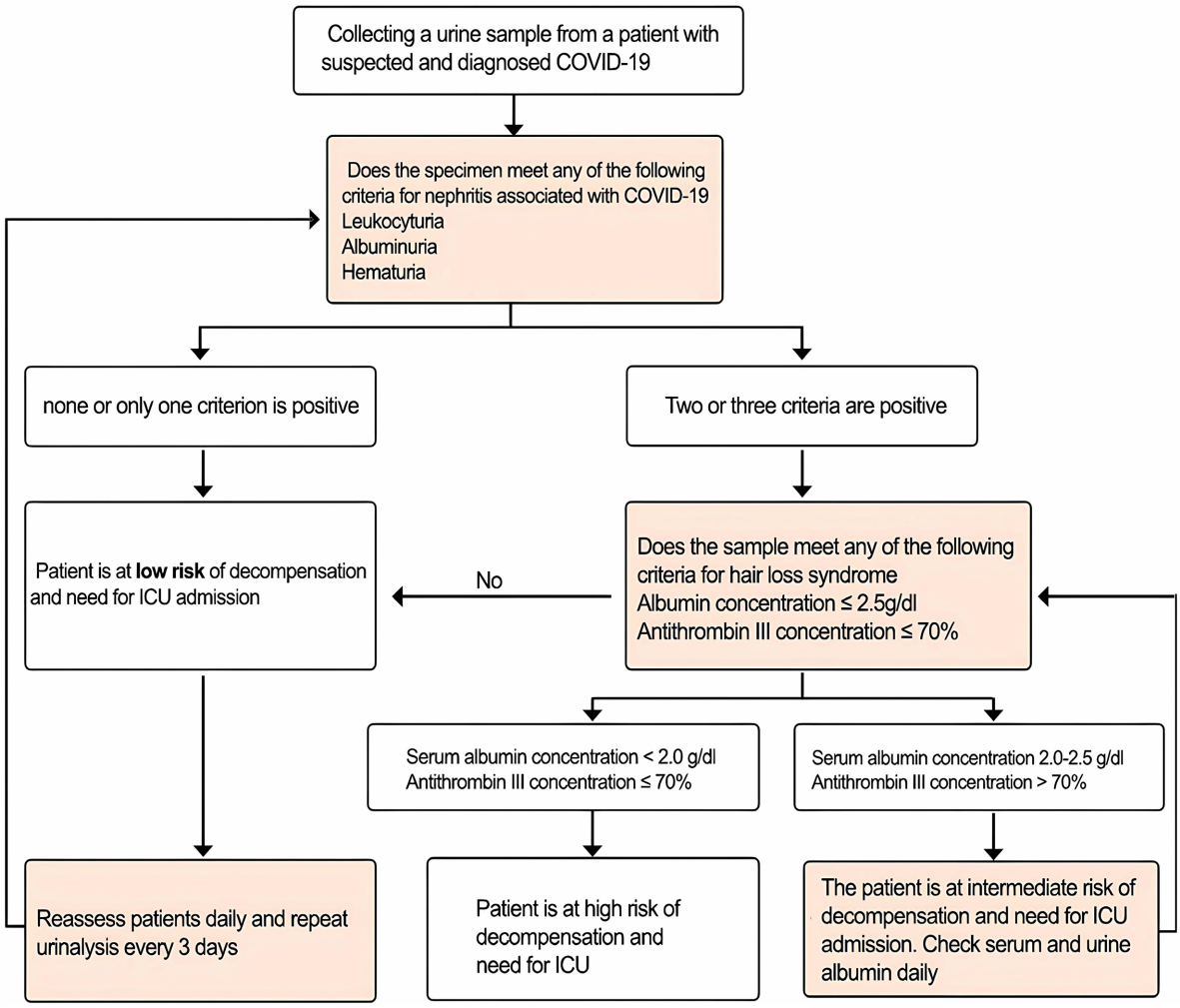

Figure 1. Proposed algorithm for the detection of nephritis associated with COVID-19 and ICU admission [10].

Patients with 2 or 3 nephritis criteria and serum albumin concentrations are between 20 and 25 g/l, were at intermediate risk of decompensation. Daily measurement of albuminemia and micro-albuminuria seemed useful for this group. This is the case of our patient.

Patients with three positive nephritis criteria and albumin concentrations below 20 g/l, must be admitted urgently to the ICU since they present a severe form of COVID-19 disease with a high risk of decompensation.

Only fluid resuscitation has been shown to be effective in halting or slowing the progression of an SFCS flare [2]. Most episodes resolve on their own within 4 days [1].

The clinical and biological condition of our patient had improved after 5 days.

4. Conclusion

Viral infections are the most common infectious causes of SSCLS. In the event of COVID-19 infection, the appearance of hypotension and hypoalbuminemia, with the gradual onset of generalized edema should suggest CFS. To better understand the underlying mechanisms of SCLS and its association with COVID-19, further research is warranted.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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