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## **SARS-CoV-2 Induces Acute and Refractory Relapse of Systemic Capillary Leak Syndrome (Clarkson's Disease)**

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1 **TITLE:** SARS-CoV-2-induces acute and refractory relapse of systemic capillary leak syndrome  
2 (Clarkson's disease)

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1 To the Editor,

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3 The systemic capillary-leak syndrome (SCLS), also known as Clarkson's disease, is a  
4 rare condition characterized by recurrent episodes of capillary hyperpermeability in the  
5 context of a monoclonal gammopathy<sup>1</sup>. We have previously shown that prophylactic  
6 treatment with intravenous immunoglobulins (IVIg) significantly reduces relapse and  
7 improve survival<sup>2,3</sup>. SCLS episodes are thought to have an infectious trigger, especially  
8 mediated by viruses and a flu-like viral syndrome was reported in more than half of the  
9 episodes in a large cohort of Clarkson's disease flares<sup>4</sup>.

10 A 45-year-old woman, with a 7-year history of IgG Kappa monoclonal gammopathy-  
11 associated SCLS, was recently admitted to our hospital for a planned immunoglobulin  
12 infusion. She regularly received IVIg since her diagnosis of Clarkson's disease at an initial  
13 dosage of 2g/kg, with progressive tapering to 0.5g/kg of body weight monthly. This  
14 preventive treatment protected her from having any relapse. When she was admitted in  
15 March 2020 she complained about nausea and vomiting and a 10 kg increase of body  
16 weight. She had no fever or any respiratory symptoms, but hypotension (80/40 mmHg) with  
17 elevated heart rate (110 bpm). Laboratory findings were typical for an acute episode  
18 (hemoglobin 19.1 g/dL, proteinemia: 42g/L). Evolution was unfavorable with severe  
19 hypovolemic shock, multiple organ failure and 4-limb compartment syndrome cumulating  
20 into refractory cardiac arrest. SARS-CoV-2 PCR turned out to be positive as sampled by  
21 tracheal aspiration.

22 The pathophysiology of SCLS is unknown. Whether the monoclonal component  
23 contributes to the pathogenesis of the disease and the mode of action of IVIg remains  
24 elusive. Still, the role of viruses as a trigger for acute relapses of the disease has repeatedly

1 been described, as holds particularly for the influenza virus. SARS-CoV-2, a novel coronavirus  
2 that spread in early 2020 from the region of Wuhan in China is characterized mainly by a  
3 severe acute respiratory distress syndrome<sup>5</sup>. In this patient, the viral infection, although  
4 poorly symptomatic, can be considered as the trigger of the relapse.

5         We believe that this report contributes to our mechanistic understanding of several  
6 urgent considerations. Firstly, our patient died from a severe episode triggered by a SARS-  
7 CoV-2 infection without demonstrating neither any signs of severe SARS-CoV-2 infection.  
8 Secondly, she did not experience any acute relapse during the previous 7 years while under  
9 preventive treatment with IVIg, yet she died after being infected with this new pandemic  
10 virus. Obviously, IVIg preparations contain virus-specific immunoglobulins that may protect  
11 patients with Clarkson's disease against seasonal viral infections. Yet, in the setting of this  
12 new pandemic virus, the protection generally granted by IVIg may vanish because of the lack  
13 of SARS-CoV-2 specific immunoglobulins in available preparations. Thirdly, conversely an  
14 additional aspect of the immunoglobulin treatment in our patient might have been  
15 insufficient to prevent such a virulent virus, i.e. the individual dosage. Therefore, an  
16 intensified IVIg treatment using increased dosages in all Clarkson's disease patients (2g/kg  
17 monthly) should be considered at least during the beginning of the pandemic. Lastly, SCLS  
18 patients should be considered at very high risk for an acute relapse while facing this new  
19 coronavirus and maximal isolation should imperatively be advocated.

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