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

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Manuscript word count: 508/500

Reference count: 5/5

Funding: None

All had access to the data and a role in writing the manuscript.

The authors have no conflict of interest to declare

To the Editor,

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

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

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

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

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

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