Clarkson's Disease Episode or Secondary Systemic Capillary Leak-Syndrome

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That Is the Question!

To the Editor:

We read with great interest the article by Case et al[1] titled "Systemic Capillary Leak Syndrome secondary to COVID-19." The authors described a fatal systemic capillary leak syndrome (SCLS) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. They suggest SCLS could be a varied presentation of the multisystemic inflammatory syndromes (MIS) associated with the coronavirus disease 2019 (COVID-19).

We recently reported a SARS-CoV-2-induced crisis of a patient with a 7-year history of IgG Kappa Clarkson's disease,[2] and several articles lately highlighted the role of lung capillary leakage in the pathophysiologic condition of COVID-19.[3]

These data suggest that COVID-19 can induce both Clarkson's disease episodes (henceforth primary SCLS) and secondary SCLS. Several considerations must be addressed to determine the nature of the capillary-leak syndrome in the reported patient.

First, COVID-19-related MIS usually affects children or young adults[4] while Clarkson's disease patients are typically >50 years old. Second, this case is highly typical of primary SCLS: very marked hemoconcentration (>20 g/dL), rapid clinical evolution, and 4-limb compartment syndrome. On the contrary, secondary SCLS usually exhibit incomplete capillary-leak syndrome with less obvious hematocrit level increase and evolves more chronically with unresolving anasarca. Third, although not reported by the authors, the presence of a monoclonal gammopathy is critical to differentiate primary or secondary SCLS.[5] Fourth, inflammatory biomarkers could be useful to distinguish the two hypotheses: being very elevated in MIS but low in primary SCLS episodes (personal data). Fifth, 80% of patients with COVID-19-related MIS had a positive serologic assay,[4] which suggests that MIS occurs in the late phase of COVID-19. However, the authors do not report how the diagnosis of SARS-CoV-2 was done. Last, therapeutic interventions (corticosteroids, IV immunoglobulins) seem to be effective in COVID-19-related MIS, although no treatment has shown its efficacy during primary SCLS severe episodes. Yet, chronic treatment with IV immunoglobulins prevents relapse and improves survival of patients with Clarkson's disease.[5]

In conclusion, COVID-19 seems to be responsible for both primary and secondary SCLS. In our opinion, the type of capillary-leak syndrome that affected the reported patient remains unclear. Differentiating the two syndromes is crucial because it has very significant therapeutic implications.

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