



Comments to: A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression

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To the Editor:

We reviewed the excellent systematic article published by Pola et al. [1] about the pathological findings in COVID-19. Based on the 250 COVID-19 autopsies found during our systematic review through March 30, 2020; we concur with the article hypothesis of mechanisms of infection and the tissular injury. However, we would like to highlight two topics that the authors did not discuss.

The first, the autopsies findings could support the hypothesis of macrophages hyperactivation. This has already been reported in other coronavirus such as SARS-CoV1 and MERS [2]. In the initial autopsies in COVID-19 patients, the presence of CD68+ macrophages in lung and heart tissues [3, 4] and the presence of CD169+ macrophages in lymph node subcapsular spaces and in splenic marginal zone were reported. These macrophages expressed the SARS-CoV-2 entry receptor ACE2 and contained SARS-CoV-2 nucleoprotein [5]. Disorders of macrophages as secondary hemophagocytic lymphohistiocytosis (sHLH) have been reported in COVID-19 [6, 7]. In autopsies, hemophagocytosis has been observed in lung, lymph node, bone marrow, liver, and spleen [6, 8–10]. sHLH is a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is mostly triggered

by viral infections, autoimmune diseases and neoplasms [11], and occurs in 3.7–4.3% of sepsis cases [12]. The diagnosis of sHLH is based on clinical, laboratory, and morphologic criteria. The main features are: unremitting fever, cytopenias, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia [13, 14]. Severe COVID-19 could be considered a hyperferritinemic syndrome by the clinical similarities detected [15]. In these conditions, Ferritin plays a critical role in the immune response. The production and secretion of extracellular ferritin is derived from macrophages [16].

The second is the presence of orchitis associated with fibrin microthrombi in COVID-19 patients [10, 17]. This condition has also been reported in cases with SARS-CoV-1 and in other viral infections like hepatitis B and C, mumps, Epstein–Barr virus, HIV, and HPV [18]. The mechanism of orchitis in SARS-CoV-2 is possibly related to the interaction of the virus with the ACE2 receptor. This receptor is expressed in spermatogonia and Leydig and Sertoli Cells [19]. We believe the relationship between hormone levels and testicular compromise deserve further study. Ma et al. reported 81 patients with COVID-19 with testosterone to luteinizing hormone (T to LH) ratio dramatically decreased in comparison with 100 healthy males ($p < 0.0001$) [20].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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