Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

A plea for the pathogenic role of immune complexes in severe Covid-19

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A comprehensive picture of the immunopathological events that occur after infection by SARS-CoV2 is progressively emerging, with distinct features in benign *versus* severe cases and at earlier *versus* later stages of infection. For the first time, however, the involvement of immune complexes (ICs) in the pathogenesis of severe cases of Covid-19 is evoked in the review article by Felsenstein et al. that we have read with great interest [1]. Most of the recent clinical and immunological studies performed in patients with severe Covid-19 have focused on the secondary burst of massive inflammation, at the primary site of infection in the lung, and also in other organs such as the kidney and the cardio-vascular or neurological systems, associated with the Cytokine Release Syndrome (CRS), commonly designated as a 'cytokine storm' [2]. The relatively low percentage of severe Covid-19 in patients with chronic inflammatory disorders treated by powerful inflammatory cytokine inhibitors [3], as well as encouraging preliminary results with anti-IL6 agents such as tocilizumab [1] indicate that preventing or treating the CRS may prevent or treat a number of severe clinical forms of Covid-19. However, why does the CRS occur only in a proportion of patients? What is the *primum movens* of the phenomenon? What are the mechanisms that make the link between the CRS and the recognized risk factors of severe Covid-19 (older age, male gender, hypertension, diabetes)? These questions are still unanswered. As rightly outlined by Felsenstein et al., ICs have to be seriously considered among the potential determinants of the CRS [1]. This hypothesis is justified by the delayed occurrence of the cytokine storm and patient's aggravation, pathological observations of endothelitis, association with disseminated microvascular thrombosis in the most severe cases, and location of the lesions to specific organs, including heart, brain, kidney and skin [1,4]; similar observations are common in experimental and clinical models of pathogenic ICs, such as serum sickness, or viral diseases with IC deposition and massive inflammatory reactions [5]. In the recent weeks, observations of intravenous immunoglobulins- (Igs-) responsive Kawasaki-like disease in children with SARS-CoV2 infection [6] and the efficacy of IL-1 receptor antagonist (anakinra) in a severely ill COVID-19 teenage patient [7] were published. Both add new arguments to the hypothesis, the former in view of the documented association of the Kawasaki syndrome with IC formation and deposition [8] and the latter because the authors showed that high inflammatory markers were associated with pathologically low levels of C3 and C4 Complement components. The first report of Covid-19 treated with the Complement C3 inhibitor AMY-101 paves the way towards a new therapeutic approach which also strongly supports our hypothesis [9].

Historical studies on serum sickness focused on the circumstances of IC disease occurrence and stressed the triggering effect of differences in hydrostatic pressure and vasoactive changes in microvessels to enhance IC deposit, inflammatory reaction, endothelitis and microthrombosis [5]. In SARS-CoV2 infection, the particular property of the virus to bind ACE2 [1], an enzymatic inhibitor of angiotensin II, able to modify the local microenvironment of ICs in vessels and alveoli, could be a trigger factor for IC-related endothelitis. Previous microvascular alterations, as those seen in arterial hypertension or diabetes which are well-recognized factors for Covid-19 severity [4], may also favor pathogenic deposits of ICs with subsequent inflammation. The elegant pathological analyses performed in selected cases of Covid-19 highlighted critical alterations of the endothelial cells in relation to the presence of the virus, suggesting a role of virus-receptor interaction [10]. However, as far as we know, the non-mutually exclusive hypothesis of an involvement of ICs was not ruled out. Although viral RNA detection in endothelia may indicate a role for direct virus pathogenicity in microvessels, it does not exclude that viral material may only be a part of pathogenic ICs in various organs.

Historical experimental studies also demonstrated that the properties and pathogenicity of ICs are altered by antigen-antibody ratio, and occurrence of serum sickness has generally been observed in 'antigen excess' [5]. Thus, the corresponding figure may vary during the course of the infection and according to the maturity of the immune system in children or its decline in aging individuals [1]. Therapy with plasma from Covid-19 patients after recovery could, in addition to its suggested role by providing neutralizing antibodies, play a role by modifying the antigen/antibody ratio that would be crucial for the beneficial *versus* pathogenic nature of ICs. By analogy with Kawasaki disease, individual susceptibility may be, at least partially, related to variants of genes involved in B cell-related immunity (*e.g. BLK*, *CD40/CD40L*, and *FCGR2A* genetic variants) [8].

The specific humoral and cellular immune response towards SARS-CoV2 was comprehensively analyzed in a non-severe case of the disease [11]. More recently antibody follow-up was performed in patients with mild symptoms and critically ill patients, showing differences between

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the two clinical forms of Covid-19 [12]. However, very few of the published reports refer to classical indicators of IC-related diseases, such as Complement components, and in the case of renal involvement [8] Complement and Ig deposits in renal tissue and their relationship to the glomerular basement membrane were not documented. Measurement of Complement consumption and of components of the Complement activation cascade might provide clues to the demonstration of IC involvement, which could receive more conclusive support from their identification in pathological samples when available. Genetic susceptibility related to abnormal regulation of the classical and alternative pathways of Complement activation should also be explored. In addition, identification of ICs by simple techniques such as PEG-precipitation, followed by the characterization of their viral and Ig content using mass spectrometric-based proteomic techniques [8], could provide evidence for their role in the CRS associated with SARS-CoV2 infection.

In the same line as the follow-up of anti-SARS-CoV2 antibodies and their isotypes (including IgA, because of the mucosal nature of the viral infection) that of Complement components, combined with non-invasive diagnosis of endothelitis and micro-thrombosis by imaging, could help predict IC-related events in a given patient. Documenting the status of ICs in Covid-19 may also be critical for the design and time management of immune-based treatments such as plasma therapy and vaccine.

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Declaration of Competing Interest

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