Correspondence on 'Anticardiolipin and other antiphospholipid antibodies in critically ill COVID-19 positive and negative patients' by Trahtemberg *et al*

I read with great interest the article by Trahtemberg *et al*[1] on the clinical relevance of antiphospholipid antibodies (aPLs), in particular anticardiolipin antibodies (aCLs), in critically ill COVID-19 positive and negative patients. Severe COVID-19 is associated with a hypercoagulable state. Early studies identified the presence of aPLs in critically ill COVID-19 patients,[2] which has attracted considerable attention as the presence of aPLs is one of the mechanisms leading to coagulopathy. Substantial efforts then tried to associate the thrombotic events seen in COVID-19 to aPLs status. The results seem negative, but a number of different types of autoantibodies were identified.[3] Chang *et al* recently reported that autoantibodies were present in approximately half of the hospitalised patients with COVID-19 but in less than 15% of healthy controls.[4] In addition to aCLs and anti-beta 2 glycoprotein 1 antibodies (aβ2-GP1), they also identified autoantibodies targeting autoantigens associated with rare disorders such as myositis, systemic sclerosis and overlap syndromes as well as targeting interferons/interleukins and other cytokines.[4] These findings suggest that COVID-19, in particular patients with severe/critical conditions, displayed certain autoimmune features.

In the well-designed study by Trahtemberg *et al*, the authors expanded the cohort by including COVID-19 negative patients with acute respiratory failure who were admitted to intensive care unit (ICU). They found that aCLs were present in 59% severe COVID-19 patients but were also detected in 35% contemporaneous non-COVID-19 patients. They also identified the presence of a broad range of non-antiphospholipid syndrome autoantibodies as well as anticytokine autoantibodies. Specifically, over 50% patients were positive for antinuclear antibodies (ANA), and 38% patients were positive for anticytokine autoantibodies.[1] These findings thus confirmed and extended previous observations that the autoimmune feature may be not restricted to severe COVID-19 but may be a common feature of severe respiratory diseases.

aPLs can be induced in a number of virus infections, but ANA and other autoantibodies are normally absent.[5] However, a broad range of autoantibodies, in particular ANA, are present in severe COVID-19, rendering the severe COVID-19 more resemble of a systemic autoimmune disease. In fact, by detailed characterisation of B cell responses through high-dimensional flow cytometry, Woodruff *et al*[6] have found that the immunological landscape associated with effector B cell mobilisation in COVID-19 is highly similar to the one observed in patients with active autoimmune processes and in particular with active systemic lupus erythematosus (SLE). Instead of predicting thrombotic events, the autoimmune features may be associated with disease severity. Trahtemberg *et al*[1] found that the presence of aCLs was associated with more severe disease independent of COVID-19 status, which is consistent with the findings by Woodruff *et al*, who have found that disease severity and poor clinical outcomes of COVID-19 are closely correlated with intense activation of the extrafollicular B cell pathway that leads to the generation of autoreactive antibody-secreting cell responses.[6] Multiple tissues/organs damage due to widespread and overwhelming inflammation (ie, cytokine storm) during severe COVID-19 may result in excessive generation and accumulation of autoantigens,[7] which could boost production of autoantibodies that had previously existed at very low levels in the body.

Although Trahtemberg *et al*'s work provide critical insights that transient breakage of immune tolerance and the generation of autoantibodies may be a common phenomenon in severe viral infections, a number of questions need to be answered in furture studies. For example, the presence of autoantibodies in COVID-19 displayed substantial heterogeneity in terms of types and titres. For example, Trahtemberg *et al*[1] failed to detect aβ2-GP1 in patients with COVID-19, but other studies reported the existence of these aPLs.[2 4 8 9] Xiao *et al*[9] showed that the levels of aPLs rapidly decreased after hitting the peak. It seems that the emergence of autoantibodies is due to a sporadic loss of self-tolerance. It thus remains unknown when aPLs first emerged and the chronological order of the emergence of different aPLs. It also remains unclear whether ANAs and other autoantibodies (ie, anticytokine antibodies) follow the similar pattern. The timing of sample collection seems an important factor. Second, COVID-19 and some autoimmune disorders (ie, SLE or antiphospholipid syndrome) share some clinical and laboratory similarities. It has been reported that some patients develop autoimmune diseases, such as Guillain-Barre syndrome or SLE, after COVID-19 infection.[10] It is thus unclear whether or not COVID-19 infection accelerates the pathological process in these predisposed subjects or just a coincidence. Third, it remains to be determined whether or not vaccinated subjects develop autoantibodies after being infected by SARS-CoV-2, especially in those who have severe COVID-19.

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