Long COVID-19 syndrome: association of cardiopulmonary impairment with a persistent platelet activation

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Background: A considerable proportion of patients do not fully recover from COVID-19 infection and report symptoms that persist beyond the initial phase of infection: this condition is defined long-COVID-19 syndrome (LCS). LCS can involve lungs as well as several extrapulmonary organs, including the cardiovascular system. The risk and 1-year burden of cardiovascular diseases (CVD) is increased in COVID-19 survivors, even in subjects at low risk of CVD. Recently, we documented that acute COVID-19 infection induces altered platelet activation state characterized by a prothrombotic phenotype and by the formation of platelet-leukocyte aggregates (PLA), that may be involved in the pulmonary microthrombi found in autoptic specimens. No data are yet available on the contribution of platelet activation to residual pulmonary impairment and procoagulant potential in LCS patients.

Purpose: To study platelet activation status, microvesicle (MV) profile, platelet thrombin generation capacity (pTGC) in LCS patients enrolled at 6 months after resolution of the acute phase (6mo-FU), compared to acute COVID-19 infection patients.

Methods: 6mo-FU COVID-19 patients (n=24) with established LCS were enrolled at Centro Cardiologico Monzino. Residual pulmonary impairment was assessed by Cardiopulmonary Exercise Testing (CPET) and 64-rows-CT scan evaluation. Platelet activation (P-selectin, Tissue Factor [TF] and PLA) and MV profile were assessed by flow cytometry; pTGC by calibrated automated thrombogram. 46 patients enrolled during acute COVID-19 infection and 46 healthy subjects (HS) were used for comparison.

Results: Dispnea in LCS patients was confirmed by CPET showing compromised alveolus-capillary membrane diffusion and residual pulmonary impairment. TF+-platelet and -MV levels were 3-fold (1.5% [1.2–2.9] vs 2.4% [1.6–5.7]) and 2-fold (217/μl [137–275] vs 435/μl [275–633]) lower at 6mo-FU compared to acute phase, being comparable to HS. pTGC behaved similarly. At 6mo-FU, the MV profile, in terms of total number and cell origin, returned to physiological levels. Conversely, although lower than that measured in acute phase, a 2.5-fold higher platelet P-selectin expression (6.9% [3–13.5] vs 11.7% [5.2–18.9]) and PLA formation (35.5% [27.4–46.8] vs 67.7% [45.7–85.3]) was observed at 6mo-FU compared to HS. Interestingly, a significant correlation between PLA formation and residual pulmonary impairment was observed (r=–0.423; p=0.02).

Conclusion: These data strengthen the hypothesis that the presence of PLA in the bloodstream, and thus also in the pulmonary microcirculation, may contribute to support pulmonary dysfunction still observed in LCS patients.