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Letter to the Editors-in-Chief

Invited commentary to: ADAMTS13 deficiency is associated with abnormal distribution of von Willebrand factor multimers in patients with COVID-19 by Tiffany Pascreau et al. Letter to the Editors-in-Chief, Thrombosis Research

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is the cause of a world-wide pandemic that has caused more than 2.5 million deaths worldwide as of mid February 2021 since its onset in December 2019. Severely affected patients suffer from pneumonia, necessitating invasive ventilation and several groups showed a high incidence and prevalence of venous and arterial thromboembolic events of large vessels and also microvascular thrombosis of the pulmonary circulation [1–3]. Hemostatic laboratory parameters at admission of COVID-19 patients, especially strongly elevated D-dimer levels, were predictive of mortality [4]. Tang et al. described that 15 of the 21 non-survivors among 183 consecutive patients with COVID-19 pneumonia fulfilled the ISTH criteria for overt disseminated intravascular coagulation (DIC) [5], whereas DIC was present in only 1 of 162 survivors [6]. Diagnosis of DIC in these patients was based on often strongly increased D-dimers, mildly/moderately prolonged prothrombin times and often mild thrombocytopenia [6]. In contrast to typical DIC associated with bacterial sepsis, obstetrical complications and other inflammatory conditions, fibrinogen levels in COVID-19 are mostly highly elevated and rarely fall below the critical limit of 100 mg/dL and thrombocytopenia is often mild or lacking [7,8]. Several authors suggested that the hemostaseologic alterations in COVID-19 together with autopsy and histopathologic findings reflected a form of thrombotic microangiopathy (TMA) rather than DIC [9–12]. Direct endothelial invasion by SARS-CoV-2 resulting in endothelial cell apoptosis [13], severe alveolar damage with occlusion of the pulmonary microcirculation [10,14–16] by fibrinous microthrombi [14–16], distinctive features of abnormal new vessel growth with intussusceptive angiogenesis [15], and deposition of complement activation products hinting at activation of the alternative and lectin based complement pathways [16] were reported in autopsy studies. Besides predominant pulmonary involvement, microvascular injury to the skin was observed in histopathologic studies of biopsies of COVID-19-associated skin rashes [16].

Compatible with severe endothelial damage, several authors noted marked elevations of Von Willebrand factor activity (VWF:act), VWF antigen (VWF:Ag) and factor VIII clotting activity (FVIII:C) in COVID-19 patients [7,8,11,17–20] and some found low normal or mildly decreased ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif, number 13) activity [8,9,11,18–20]. The VWF:Ag/ADAMTS13 activity ratio was strongly elevated in these studies [8,11,18,20].

In this issue of Thrombosis Research, Pascreau et al. present a single tertiary care center study on 70 patients with COVID-19 pneumonia of variable severity ($n = 4$, treated as outpatients; $n = 44$, needing hospitalization on non-intensive care units; and $n = 22$, needing treatment on intensive care units) [21]. These authors are to be congratulated for having performed a systematic study on the ADAMTS13-VWF axis in a large number of COVID-19 patients. VWF:act and VWF:Ag levels were significantly increased and the VWF:act/VWF:Ag ratio was slightly lower in both non-ICU and ICU patients with COVID-19 as compared to healthy controls. ADAMTS13 antigen values, on the other hand, were significantly lower in hospitalized COVID-19 patients than in controls, whereby the ICU patients tended to have lower ADAMTS13 antigen than the non-ICU patients (no significant difference). The ADAMTS13:Ag in the 70 patients correlated negatively with the VWF:Ag and also with C-reactive protein. In a subgroup of 10 patients, Pascreau et al. analyzed the VWF multimeric distribution using the commercial Hydragel 5 von Willebrand factor multimer kit (Sebia) and found a relative decrease of high molecular weight VWF multimers and a relative increase of intermediate and low molecular VWF multimers in 8/10 patients [21]. This imbalance of a markedly increased VWF and moderately decreased ADAMTS13 levels with an elevated VWF/ADAMTS13 ratio is suggested to represent a «consumption» of ADAMTS13 by the massively increased VWF and proposed to contribute to the pulmonary microthrombi formation [21]. The authors note that in contrast to the disease thrombotic thrombocytopenic purpura (TTP), defined by a very severe autoantibody-mediated or congenital deficiency of the ADAMTS13 [22,23], the hallmarks of severe thrombocytopenia and microangiopathic hemolytic anemia are lacking in almost all COVID-19 patients [7,8,20]. Also, the thrombi of the pulmonary microcirculation have mostly been reported as predominantly “fibrinous” [14–16], even though Fox et al. suggested the presence of platelets and VWF in the microthrombi of pulmonary alveolar capillaries by immunostaining [24].

Pascreau et al. [21] as well as other investigators [9,11,18,20] propose that the VWF-ADAMTS13 dysbalance may be causally related to the prothrombotic tendency and the (predominantly pulmonary) microvascular thrombosis. Based on this hypothesis, it is proposed that supplementation of ADAMTS13 [21] or the use of caplacizumab blocking the VWF A1 domain interaction with platelet glycoprotein Ib-alpha might be useful therapeutically in severe COVID-19 [11]. Caplacizumab has been found efficacious as an adjunctive therapy to plasma exchange, fresh frozen plasma replacement and immunosuppression in patients suffering from acute autoimmune TTP with severe acquired ADAMTS13 deficiency, resulting in a faster normalization of the severely decreased platelet count as compared to placebo [25,26]. Nevertheless, in Covid-19 patients there is mostly no severe thrombocytopenia and no microangiopathic hemolytic anemia [8,20] which are the diagnostic hallmarks of classic TMAs [22].

We offer the following pathophysiologic hypothesis: the severe endothelial damage caused by direct SARS-CoV-2 invasion leads to

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profound and prolonged release of VWF from endothelial storage sites, the Weibel-Palade-bodies. The ADAMTS13 is partially trapped to the endothelial surface where it cleaves the nascent unusually large VWF on the endothelial surface [27] resulting in a mild to moderate decrease of circulating ADAMTS13 similar to the situation in severe sepsis or septic shock [28] or, as a short-lived phenomenon, after excessive VWF release induced by endotoxin or desmopressin application in healthy volunteers [29]. This is compatible with the highly significant negative correlation of the ADAMTS13 antigen with increasing VWF antigen as shown by Pascreau et al. in 70 COVID-19 patients [21] and the mildly decreased ADAMTS13 could represent a mere epiphenomenon. The widespread thrombi in the pulmonary microcirculation consist mainly of fibrin [14–16] similar to the predominantly renal microthrombi in hemolytic uremic syndrome [30]. The strongly elevated FVIII:C levels in severe COVID-19 [7,19] may enhance thrombin and fibrin generation. The fact that COVID-19-associated coagulopathy with its predominantly pulmonary thrombotic microangiopathy is not accompanied by severe thrombocytopenia and intravascular red blood cell fragmentation with schistocytes [8,20], in contrast to the classic TMAs such as TTP or HUS [22], may hypothetically be due to the much lower blood pressure gradient in the pulmonary as compared to the peripheral arterial circulation [8]. Certainly, this hypothesis needs further confirmation.

Declaration of competing interest

B.L. is Chairman of the Data Safety Monitoring Committee of the BAXALTA 281102 and the SHIRE SHP655-201 studies (now both run by TAKEDA), investigating recombinant ADAMTS13 therapy in hereditary and acquired TTP, respectively. He is on the Advisory Board of Sanofi for caplacizumab, and received travel and accomodation support for participating at scientific meetings and/or lecture fees from Ablynx, Alexion, Bayer, Roche, Sanofi and Siemens.

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