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Etiology and Management of Bleeding during ECMO in a COVID-19 Patient

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We read with great interest the manuscript by Hayakawa *et al.* about the management of a coronavirus disease 2019 (COVID-19) patient with acquired von Willebrand syndrome (AVWS) during extracorporeal membrane oxygenation (ECMO)[1]. In that case, the authors focused on the involvement of AVWS as a cause of bleeding in COVID-19 patients treated with ECMO. They also drew attention to the complication of disseminated intravascular coagulation (DIC) in this case. We want to focus on the characteristic points of DIC as evident from the case description.

In general, DIC is classified into three types based on the degree of fibrinolytic activation. As for enhanced-fibrinolytic-type DIC in which bleeding symptoms are likely to appear, plasma levels of thrombin-antithrombin (TAT) complex ≥ 20 μg/L (reference: <4.0 μg/L) and levels of plasmin-α_2 plasmin inhibitor complex (PIC) ≥ 10 μg/mL (reference: <0.8 μg/mL) have been proposed by Asakura[2]. In fact, plasma levels of PIC are around 10 μg/mL in many cases of enhanced-fibrinolytic-type DIC[3, 4]. Even in acute promyelocytic leukemia, which is a typical underlying disease for enhanced-fibrinolytic-type DIC, plasma levels of PIC are around 10 μg/mL[2]. In the case described, plasma levels of TAT and PIC had increased significantly before the discontinuation of ECMO and unfractionated heparin[1]. In particular, the PIC level was extremely high in this case (20 μg/mL). We considered that the patient showed enhanced-fibrinolytic-type DIC at that time. Since plasma levels of PIC during ECMO without circuit clot were 0.9 μg/mL and with circuit clot were 4.4 μg/mL[5], such a significant rise in PIC level was rarely encountered[1]. After this substantial increase, PIC levels sharply decreased. We are very interested in the interpretation of this dramatic change and the levels of α_2 plasmin inhibitor (α_2PI) at that time, as marked depression of α_2PI is an indicator of bleeding risk[2]. As the authors pointed out, AVWS alone could not explain this data, and the complication of DIC was certain.

In the future, when encountering bleeding during ECMO, looking for a significant increase in FDP levels and dissociation between FDP and D-dimer is thought to represent a simple screening strategy to distinguish bleeding caused by AVWS alone from the one that also involves enhanced-fibrinolytic-type DIC. If dissociation between FDP and D-dimer is observed, plasma levels of TAT, PIC, and α_2PI play an important role in reaching a definitive diagnosis[2].

Causes of bleeding while using ECMO with COVID-19 may include AVWS, enhanced-fibrinolytic-type DIC, adverse effects of anticoagulant therapy, and vascular fragility associated with endotheliitis[6]. If AVWS is the cause of bleeding, early discontinuation of ECMO is the best strategy to improve bleeding. If anticoagulant therapy appears too strong, reduction of the anticoagulant agents should be considered, although the risk of thrombosis (one of the main causes of death from COVID-19) will inevitably be increased. Confirmation of the cause of bleeding is thus extremely important to save COVID-19 patients using ECMO.

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The authors described the following reasons for using cryoprecipitate for AVWS in this case[1]. First, cryoprecipitate and plasma-derived VWF was considered to contain higher concentrations of VWF and lower concentrations of ADAMTS13 than fresh frozen plasma (FFP). Second, cryoprecipitate contains α_2 antiplasmin (an α_2 plasmin inhibitor), which acts to suppress fibrinolysis and is considered effective for enhanced-fibrinolytic-type DIC. Plasma-derived VWF may also only be effective for a short period because of the high shear stress present inside the ECMO pump. In recent years, recombinant human von Willebrand preparation (Vonicog alfa; Shire Japan, Tokyo, Japan)[7] has been launched in Japan, and its efficacy against AVWS needs to be evaluated. The authors described using cryoprecipitate to supplement α_2 antiplasmin for fibrinolysis suppression.

When using ECMO in COVID-19 patients, anticoagulant therapy with heparin and an antifibrinolytic agent should be performed at the same time when enhanced-fibrinolytic-type DIC is present as a complication, as in this case. In other words, heparin used with nafamostat (an anti-thrombin agent that also has strong inhibitory effects on fibrinolysis) can be expected to prove effective[6, 8]. Furthermore, nafamostat is not only effective against enhanced-fibrinolytic-type DIC, but also shows anti-SARS-CoV-2 activation[9, 10]. Nafamostat is thus a promising agent for COVID-19.

Finally, the report by Hayakawa *et al.* is valuable because they performed a detailed follow-up of the coagulation markers during the course of treatment in COVID-19 patients and noted that we should pay attention to not only enhanced-fibrinolytic-type DIC, but also AVWS as a cause of bleeding when using ECMO. The treatment strategy for AVWS warrants further study. For enhanced-fibrinolytic-type DIC, we would like to suggest combined use of heparin and nafamostat.

Conflicts of Interest

None of the authors have any conflicts of interest to report.

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