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Disseminated Multifocal Intracerebral Bleeding Events in Three Coronavirus Disease 2019 Patients on Extracorporeal Membrane Oxygenation As Rescue Therapy

Karl Bihlmaier, MD, PhD[1]; Roland Coras, MD[2]; Carsten Willam, MD[1]; Steffen Grampp, MD[1]; Samir Jabari, MD[2]; Philip Eichhorn, MD[3]; Florian Haller , MD[3]; Joji Kuramatsu, MD[4]; Stefan Schwab, MD[4]; Ixchel Castellanos, MD[5]; Torsten Birkholz, MD[5]; Jürgen Schüttler, MD[5]; Jürgen Altmeppen, MD[6]; Mario Schiffer, MD[1]; Larissa Herbst, MD[1]

Objectives: To describe three coronavirus disease 2019 patients suffering from acute respiratory distress syndrome under venovenous extracorporeal membrane oxygenation therapy and tight anticoagulation monitoring presenting a novel pattern of multifocal brain hemorrhage in various degrees in all cerebral and cerebellar lobes.

Design: Clinical observation of three patients. Post mortem examinations.

Setting: Two ICUs at the University Hospital Erlangen.

Patients: Three patients (medium age 56.6 yr, two male with hypertension and diabetes, one female with no medical history) developed severe acute respiratory distress syndrome on the basis of a severe acute respiratory syndrome coronavirus 2 infection. All required mechanical ventilation and venovenous extracorporeal membrane oxygenation support.

Interventions: Clinical observation, CT, data extraction from electronic medical records, and post mortem examinations.

Main Results: We report on an unusual multifocal bleeding pattern in the white matter in three cases with severe acute respiratory distress syndrome due to coronavirus disease 2019 undergoing venovenous extracorporeal membrane oxygenation therapy. Bleeding pattern with consecutive herniation was found in CT scans as well as in neuropathologic post mortem examinations. Frequency for this unusual brain hemorrhage in coronavirus disease 2019 patients with extracorporeal membrane oxygenation therapy at our hospital is currently 50%, whereas bleeding events in extracorporeal membrane oxygenation patients generally occur at 10–15%.

Conclusions: Multifocality and high frequency of the unusual white matter hemorrhage pattern suggest a coherence to coronavirus disease 2019. Neuropathological analyses showed circumscribed thrombotic cerebrovascular occlusions, which eventually led to microvascular and later on macrovascular disseminated bleeding events. However, signs of cerebrovascular inflammation could not be detected. Polymerase chain reaction analyses of brain tissue or cerebrospinal fluid remained negative. Increased susceptibility for fatal bleeding events should be taken into consideration in terms of systemic anticoagulation strategies in coronavirus disease 2019.

Key Words: acute respiratory distress syndrome; cerebral microhemorrhage; coronavirus disease 2019; extracorporeal membrane oxygenation; intracerebral bleeding

At the University Hospital Erlangen, 33 patients with severe acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) were treated on different ICU wards, of which six received venovenous extracorporeal membrane oxygenation (ECMO) as rescue therapy. Three venovenous ECMO patients (medium age 56.6 yr) developed sudden anisocoria and absent pupillary reflexes and died shortly after. Cranial CT scans showed fatal severe multifocal intracerebral bleedings in two of the three patients localized in the white

[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany.

[2]Department of Neuropathology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany.

[3]Department of Pathology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany.

[4]Department of Neurology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany.

[5]Department of Anesthesiology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany.

[6]Department of Anesthesiology, Weiden Hospital, Weiden, Germany.

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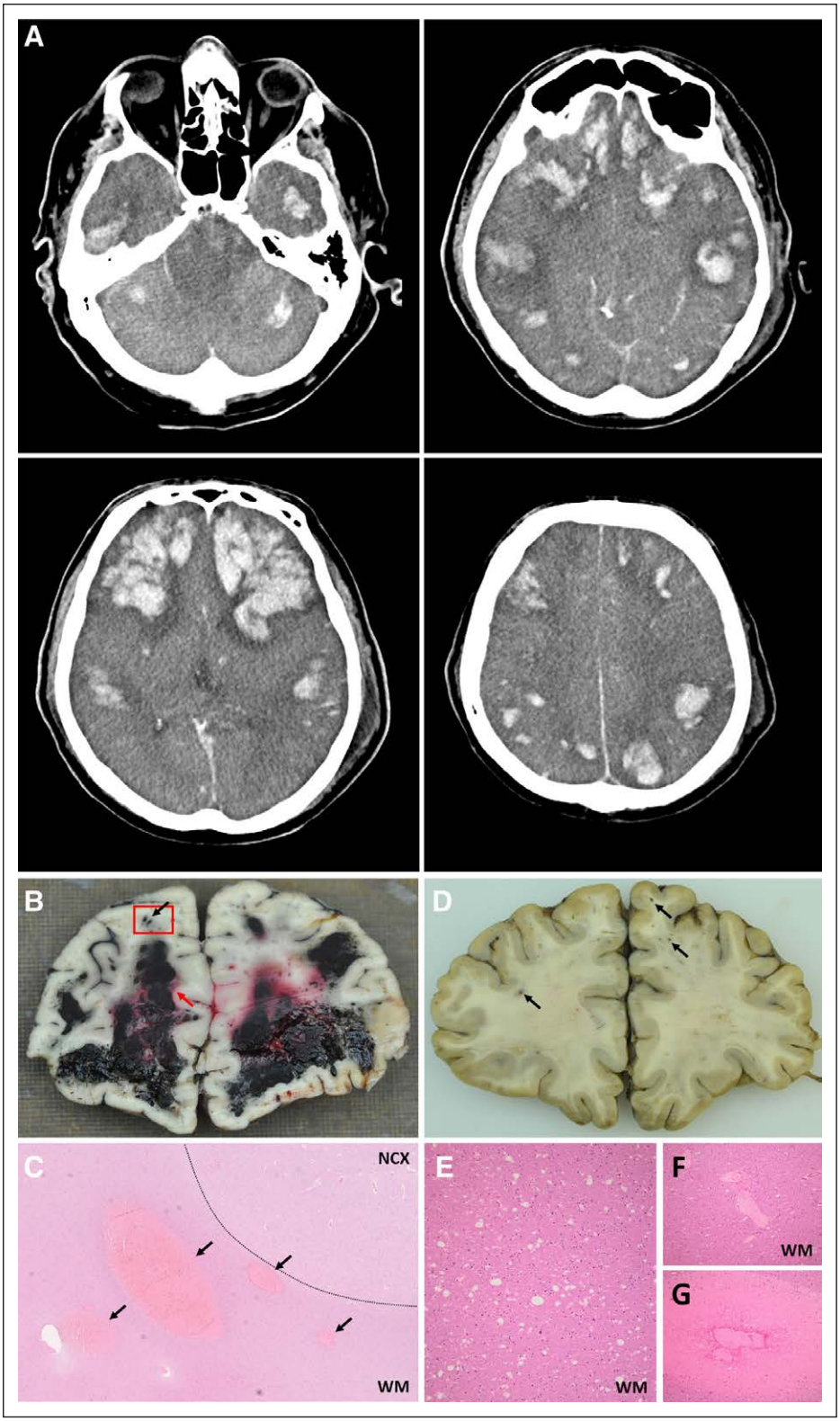

Figure 1. Radiological and histopathological findings. **A**, Cranial CT scan illustrating a simultaneous disseminated multifocal intracerebral bleeding pattern in all lobes of the cerebrum and cerebellum. **B**, Representative macroscopic slide in coronal frontal plane shows brain congestion with small bleeds (*black arrow*) as well as larger subcortical parenchymal hemorrhages (*red arrow*). Note flattening of the brain surface assign for edema. **C**, Histological examination confirms multiple petechial hemorrhages confined to the subcortical *white* matter (WM) (*black arrows*). **D**, Representative coronal slide in a patient with multiple WM congestion/microhemorrhages (*black arrows*). Histological examination shows edema confined to the WM (**E**) with congestion (**F**) as well as small hemorrhages (**G**). *Dotted line* in (**C**): *Gray* matter/WM junction. NCX = neocortex/cortical ribbon.

matter of both the cerebrum and cerebellum (**Fig. 1*A***). This extensive multifocality, partly exceeding 50 simultaneous bleeding sites, has not been described to date. Even though severe multifocal intracerebral parenchymal hemorrhage of the gray matter is occasionally found in patients undergoing ECMO therapy (1, 2), the bleeding pattern of the patients presented here appeared unusual and therefore suggestive for a potential association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or endothelialitis. A literature review on cerebral hemorrhage in COVID-19 patients revealed recent retrospective analyses and case reports describing occasional bleeding events (3–7). Here, parenchymal hemorrhage is found merely sporadic but diffuse petechial and in different lobes of the cerebrum or cerebellum. Hemorrhage etiology has been discussed but remains elusive (8, 9).

A medical history of arterial hypertension and diabetes was known in two patients; one of them used acetylsalicylic acid as antiplatelet therapy. None of the three had a history of vasculopathy or cerebral comorbidities. All patients presented signs of a hyperinflammatory state with elevated C-reactive protein levels (peak values 310–430 mg/L) and high as well as continuously rising ferritin levels (2,200–7,100 ng/mL). Nota bene raising ferritin levels are a negative predictor for the course of the COVID-19. Both patients presenting fatal hemorrhage did not show acute kidney injury as potential risk factors for cerebrovascular events.

Autopsy in two patients with fatal brain hemorrhage confirmed generalized brain edema with signs of transtentorial herniation of medial parts of the temporal lobe and transforaminal herniation of the cerebellar tonsils (**Fig. 1*B***). Both cases showed secondary Duret hemorrhages of the pons and multiple supratentorial and infratentorial subcortical fresh hemorrhages (**Fig. 1*C***). These were predominantly confined to the subcortical white matter. The prominent brain congestion and the multiple fresh hemorrhagic lesions could be confirmed on histological level at subcortical site with prominent edema of the adjacent cortical ribbon areas. Autopsy in the third patient showed regular macroscopic findings without signs for brain edema or herniation. Interestingly, on macroscopic coronal slides

and in microscopy areas with congested subcortical vessels and perivascular hemorrhagic extravasates were found (**Fig. 1*D***). Histology revealed white matter edema, most likely of vasogenic etiology with prominent congestion as well as multifocal microhemorrhages (**Fig. 1*E–G***).

There were no signs of an inflammatory process in any of the three cases. All three patients showed cerebral microangiopathy (small vessel disease) in microscopy of various degrees with hyaline mural thickening of small arteries/arterioles but also affected venules and capillaries. We suspect that the third patient represents the same pathomechanism caught at an earlier stage before macroscopic hemorrhages became evident.

Due to the atypical bleeding patterns and since brain infections of COVID-19 patients are frequently described (9–11), we hypothesized that the multifocal intracerebral hemorrhages could be attributed to a COVID-19–associated vascular pathology, for example, a cerebral endothelialitis. However, after extensive histological analysis including immunohistochemical stainings, we could not confirm any signs of leukocyte infiltrates or any other inflammatory processes, neither of the meninges, the brain parenchyma, nor of the brain vasculature.

1) Since other tissues investigated (e.g., kidney) could also not confirm signs of vascular inflammation, we cannot explain simultaneous multifocal intracerebral bleedings by vascular infiltration and inflammation. Correspondingly, in contrast to positive lung tissue, polymerase chain reaction analyses of multiple cerebral tissue samples, as well as liquor samples, remained negative for SARS-CoV-2 virus RNA. However, the small vessel angiopathy could have potentially contributed to an increased vascular vulnerability and intracerebral blood leakage, in particular, under conditions of increased venous pressure due to venovenous ECMO blood flow and systemic anticoagulation. Venovenous ECMO systems at our hospital are regularly cannulated femoro-femoral in a classic double cannulation configuration. Nevertheless, whether microangiopathy and positive hemosiderin deposits can be attributed to previous SARS-CoV-2 infection remains elusive.
2) Two of three patients received IV immunoglobulins due to hypogammaglobulinemia. The administration of immunoglobulins is clinically associated with hemorrhage, like retroperitoneal bleedings. Since dosage was low in both patients and brain hemorrhage has previously not been reported in the context of immunoglobulin administration, an association of immunoglobulins with simultaneous multifocal intracerebral bleedings is rather unlikely.
3) Thromboembolic events such as deep vein thrombosis or pulmonary embolism are frequently observed in SARS-CoV-2 infection, which led to the recommendation of systemic anticoagulation. In addition to the hemorrhages, we found circumscribed thrombotic cerebrovascular occlusions in our histological examinations.

Since coagulation disorders are associated with intracerebral hemorrhages in ECMO patients, these microinfarctions could have presumably led to secondary disseminated multifocal intracerebral bleedings. Previously, cerebral microhemorrhages were reported in ECMO patients (12–15), which interestingly have been comparable to cerebral injuries seen in high altitude brain edema (16).

At our center, approximately 100 ECMO therapies are carried out per year, with 10–15% general cumulative frequency of intracranial hemorrhages. In the subgroup of six patients suffering from COVID-19–associated ARDS undergoing ECMO support, three presented the novel hemorrhage pattern described.

Anticoagulation targets at our center are platelets above 50,000/μL, quick greater than 50%, antithrombin greater than 70%, and activated partial thromboplastin time 60–80 seconds. Data on target monitoring are shown in **Supplemental Figure 1** (http://links.lww.com/CCX/A353). We hypothesize that multifocal intracerebral coagulation events in COVID-19 patients can eventually contribute to the reported disseminated intracerebral bleeding events, and this potential side effect has to be considered under ECMO therapy and anticoagulation strategies in COVID-19 patients.

Drs. Bihlmaier and Coras contributed equally to this article.

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For information regarding this article, E-Mail: larissa.herbst@uk-erlangen.de

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