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CASE REPORT

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Anticoagulated de novo atrial flutter complicated by transitory ischemic attack in fatal COVID-19

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Abstract

SARS-CoV-2 may not only manifest as pneumonia (COVID-19) but also in other organs, including the brain (neuro-COVID). One of the cerebral complications of SARS-CoV-2 is ischemic stroke. Transitory ischemic attack (TIA) in a SARS-CoV-2 positive has not been reported. A 78-year-old poly-morbid male (diabetes, hypertension, and coronary heart disease), admitted for COVID-19, developed atrial flutter on hospital day (hd) 2. Anticoagulation with enoxaparin was started. On hd5, he experienced a TIA despite sufficient anticoagulation. The patient expired on hd28 due to multi-organ failure from sepsis due to superinfection with staphylococcus aureus. Infection with SARS-CoV-2 may be complicated by atrial flutter. Atrial flutter may be complicated by TIA despite sufficient anticoagulation, suggesting that standard anticoagulation may be insufficient to meet SARS-CoV-2-associated hypercoagulability syndrome. Forced anticoagulation and adequate antibiosis in poly-morbid SARS-CoV-2-infected patients with hypercoagulability and cytokine storm are warranted.

KEYWORDS

anticoagulation, atrial flutter, COVID-19, hypercoagulability syndrome, ischemic stroke, SARS-CoV-2

1 | INTRODUCTION

Infection with SARS-CoV-2 may not only manifest as pneumonia (COVID-19) but also in other organs, including the brain (neuro-COVID).[1] One of the central nervous system (CNS) manifestations is ischemic stroke.[2] The cause of ischemic stroke in COVID-19 patients is multifactorial. One of these causes is cardiovascular disease, which can manifest as heart failure, arterial hypertension, or atrial fibrillation/flutter, and the other is hypercoagulability syndrome, increasingly recognized as a complication of COVID-19.[3] We hereby present and discuss a COVID-19 patient who experienced a transitory ischemic attack (TIA) despite therapeutic anticoagulation.

2 | CASE REPORT

The patient is a 78 years old male with a previous history of diabetes, arterial hypertension, vascular leukoencephalopathy, and coronary heart disease, who was admitted for COVID-19, initially treated with oxygen insufflation and steroids. After he had spontaneously developed de novo atrial flutter on hospital day (hd) 2, therapeutic

anticoagulation with enoxaparin was begun. Though creatine-kinase was mildly elevated (Table 1), myocardial infarction was excluded as the cause of atrial flutter upon ECG and absence of anginal chest pain. Endocarditis was not considered. On hd5, the patient developed sudden onset hemiparesis on the right side (NIHSS 7) with spontaneous, complete recovery within 24 h. As cerebral MRI was non-informative, including time-of-flight (TOF) angiography (Figure 1), he was diagnosed with a TIA and anticoagulation was continued. As a self-limiting, non-convulsive epileptic state was considered as a differential diagnosis by the neurologist on duty, he additionally received levetiracetam (LEV) 2,000 mg/d. On hd7, the patient was tired but communicated verbally and was able to walk. Despite being seizure-free, LEV was increased to 3,000 mg/d. On hd8, the PCR for SARS-CoV-2 was still positive. On the following day, a superinfection with staphylococcus aureus was diagnosed for which he received cefazolin. Despite this regimen, inflammatory parameters further increased (Table 1), why the antibiotic treatment was switched to tazonam. On hd11, he was again tested positive for SARS-CoV-2. PCR for SARS-CoV-2 became negative on hd15. Though EEG on hd20 only showed diffuse generalized slowing without epileptiform discharges and without ever having experienced a seizure, LEV was kept. Clinical neurologic examination on hd21 revealed somnolence, mutism, and reduced Achilles tendon reflexes. Meningitis was suspected. However, cerebro-spinal fluid (CSF) investigations on hd22 were non-informative, including cell count, culture, and viral screen. Sinus venous thrombosis was excluded on hd23. Blood sedimentation rate on hd23 was 120/1 h and interleukin-6 97.5 pg/ml (*n*, <7.0 pg/ml). Sepsis was diagnosed, and renal insufficiency developed during the following days. The patient died on hd28 from multi-organ failure. Autopsy was refused by the relatives because of religious concerns.

3 | DISCUSSION

The patient is interesting for several aspects. First, the patient developed de novo atrial flutter during the infection with SARS-CoV-2. Atrial flutter in association with COVID-19 has been previously reported as a cardiac complication of COVID-19 and can be attributed to the cytokine storm, hypoxic myocardial injury, electrolyte abnormalities, plaque rupture, coronary spasm, microthrombi, or direct endothelial or direct myocardial injury by the virus.[4] Indications for a cytokine storm in the index patient were high IL6 and high blood sedimentation rate. Myocardial infarction as an alternative cause of atrial flutter was excluded. Endocarditis was not considered as causative for atrial flutter.

Second, the patient experienced a TIA. Though ischemic stroke is a well-known complication of COVID-19,[5] a TIA has, to our knowledge, not been reported in association with COVID-19. The cause of the TIA remained speculative but most likely it was due to newly detected atrial flutter or the hypercoagulability syndrome.[6] An indication for hypercoagulability in the index patient was the mildly elevated D-dimer (Table 1). Fibrinogen values were normal throughout hospitalization. On the other hand, there are also indications for hyper-fibrinolysis in COVID-19.[7] Alternative causes of TIA could be cerebrovascular disease due to diabetes or arterial hypertension, a focal epileptic seizure, or a cerebral manifestation of the SARS-CoV-2 infection. However, cerebral MRI, CSF investigations, and EEG were non-informative.

Third, the patient developed a TIA despite sufficient anticoagulation with enoxaparin. Either the patient had a source of embolism other than atrial flutter or anticoagulation was too weak for SARS-CoV-2-associated hypercoagulability syndrome. Other sources of embolism could be a ventricular thrombus,[8] disseminated intravascular coagulation (DIC) syndrome as a complication of sepsis,

TABLE 1 Relevant blood values during hospitalization

Parameter	RL	hd1	hd3	hd5	hd8	hd19	hd23	hd25	hd27
CRP	<5 mg/L	**8.8**	**6.4**	3.5	**51.3**	**196.7**	**152.7**	**136.1**	**222.5**
Leucos	3.6–10.5 G/L	5.9	5.1	4.3	5.6	4.6	7.3	7.6	7.7
Neutrophils									
Thrombos	160-370 G/L	**98**	**108**	**103**	**105**	171	219	273	328
D-dimer	<0.5 mg/L	**0.75**	nd	0.39	nd	nd	**2.25**	nd	nd
GGT	<60 U/L	32	34	**99**	nd	**183**	**227**	**187**	**177**
AP	40–129 U/L	67	59	73	nd	**203**	**205**	**201**	**199**
CK	<190 U/L	150	**408**	**318**	127	nd	nd	nd	nd

Abbreviations: AP, alkaline phosphatase; CK, creatine-kinase; CRP, C-reactive protein; GGT, gamma-glutamyl-transaminase; leucos, leucocyte count; nd, not done; RF, reference limit; thrombos, thrombocyte count. The Significance of Bold values are those values above the reference limit.

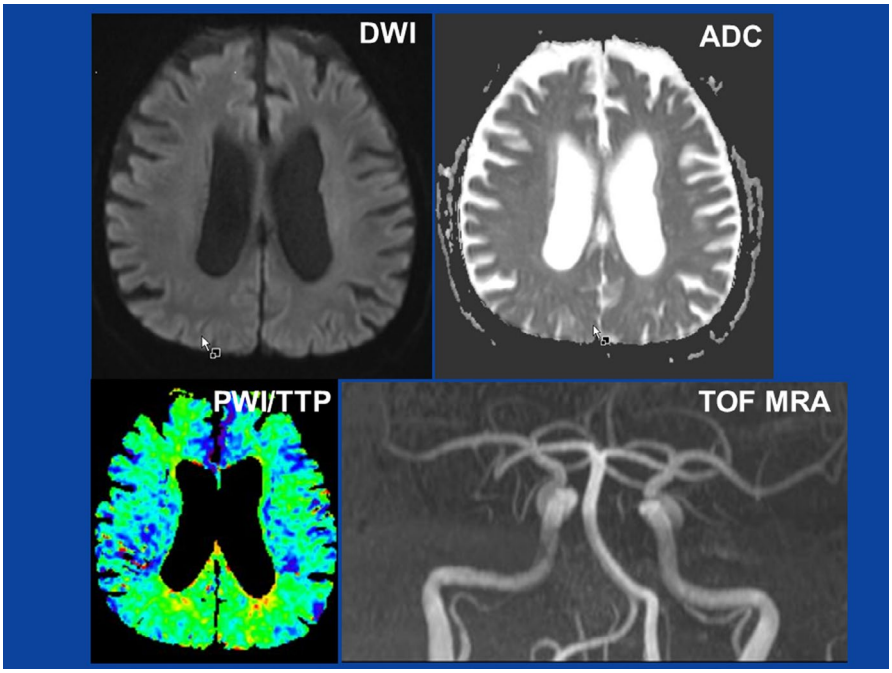

FIGURE 1 Cerebral MRI on hd5 without showing an acute lesion on diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) maps, perfusion-weighted imaging (PWI) time-to-peak, or time-of-flight angiography

or low output failure. Unfortunately, the patient did not undergo echocardiography during hospitalization. Since the patient was aseptic at the time of the TIA, sepsis is rather unlikely to have been causative. A clinical implication of the case could be to broaden the therapeutic range of the anti-factor Xa values and increase the intensity of anticoagulation.

Fourth, the patient developed superinfection with staphylococcus aureus and consecutively sepsis. Bacterial superinfection is common in COVID-19[9] and attributed to neutropenia due to sepsis or a weak humoral immune response.[10] DIC syndrome in the context of COVID-19 has been also attributed to sepsis.[10]

4 | CONCLUSIONS

Infection with SARS-CoV-2 may be complicated by atrial flutter, which may cause TIA despite sufficient anticoagulation. SARS-CoV-2 infection may be complicated by superinfection, which may lead to sepsis, DIC syndrome, multi-organ failure, and death. SARS-CoV-2-associated sepsis may mimic meningitis. The combination of sepsis-induced DIC syndrome and SARS-CoV-2-associated hypercoagulability may require forced anticoagulation and appropriate antibiosis.

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CONFLICTS OF INTERESTS
No conflict of interest declared.

AUTHOR CONTRIBUTIONS
JF: Design, literature search, discussion, first draft, critical comments, and final approval. AW: Data acquisition, literature search, discussion, and final approval. The study was approved by the institutional review board.

ETHICAL APPROVAL
Statement of ethics was in accordance if ethical guidelines.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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