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Case Report

Fatal Mesenteric Ischemia in a Severely Ill COVID-19 Patient: a Case Report

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Abstract

Background: Emerging data suggest a complex role for immuno-thrombosis in the thrombotic complications in COVID-19. We report the case of a fatal mesenteric ischemia to illustrate the mechanisms of endothelial dysfunction in the gut, and the resulting hypercoagulability.

Case Report: A 58-year-old woman was admitted in Intensive Care Unit, with initial severe acute respiratory distress syndrome due to SARS-CoV-2 pneumonia. Her respiratory status worsened, with a septic shock thirteen days after symptoms onset. The blood culture was positive with *Pseudomonas aeruginosa* and *Candida*. A rapid consecutive deterioration leading to multiorgan failure revealed colic perforation complicated with secondary peritonitis. Histopathological findings revealed small vein occlusions. Surprisingly, no SARS-CoV-2 viral particles could be detected in the bowel. We found intense endothelial dysfunction, contrasting with only mild neutrophil activation. A major increase in von Willebrand factor and resistance to fibrinolysis were the main hemostatic abnormalities.

Discussion: This case highlights that COVID-19-associated hypercoagulability can lead to early primitive thrombotic events in small vessels, and adds new evidence concerning a potential role for immuno-thrombosis. Close monitoring of endothelial dysfunction, and further consideration of new targets to prevent thrombosis by adjunctive therapies may thus appear fundamental.

Keywords: COVID-19; Mesenteric ischemia; Antiphospholipid syndrome; Endothelial activation; Hypercoagulability

Abbreviations

aPLS: Antiphospholipid syndrome; ICU: Intensive Care Unit; CT: Computed Tomography; DIC: Disseminated Intravascular Coagulopathy; DRVVT: Dilute Russell's Viper Venom Time; aPTT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; aPL: Antiphospholipid; aβ2GPI: anti-β2glycoprotein I; PE: Anti-Phoshatidylethanolamine; PS/PT: Anti-Phosphatidylserine/Prothrombin; PCR: Polymerase Chain Reaction; NETs: Neutrophil Extracellular Traps; MPO: Myeloperoxidase; vWF: von Willebrand Factor; ROTEM: Rotational Thromboelmastometry

Background

Thrombosis is frequent in critically ill COVID-19 patients [1], despite anticoagulation [2]. The risk assessment should integrate inflammation and coagulation parameters, but several observations raised the role of immunological mechanisms in the pathophysiology of thrombosis, similar to those involved in the Antiphospholipid Syndrome (aPLS) although specific antibodies are inconstantly detected [3,4]. We report a case of mesenteric ischemia in a critically ill patient with COVID-19 pneumonia, to illustrate the interactions between endothelial activation and the risk of thrombosis, and how coagulation abnormalities could be interpreted to adapt and improve the management of thrombotic complications.

Case Presentation

A 58-year-old woman, with history of diabetes, hypertension and severe obesity, was hospitalized in Dakar, Senegal on June 21st. She reported fatigue, back pain and mild fever lasting for five days. On June 25th, nine days after the onset of symptoms, dyspnea worsened dramatically. She was tested positive for SARS-Cov-2, and transferred to a local Intensive Care Unit (ICU). A referral in our institution was decided on June 28th after seven days of hospitalization without improvement, requiring invasive mechanical ventilation. She then received Remdesivir on June 29th and corticosteroids according to a randomized controlled trial protocol.

At arrival in Paris, with a PaO_2/FiO_2 ratio decreased at 92mmHg, the management required usual cares associating sedative drugs infusion, neuromuscular blockade, adequate mechanical ventilation with low-tidal volumes, inhaled Nitric Oxide for 48 hours. We didn't perform prone positioning. The hemodynamic status was stable without vasopressor support, the kidney and hepatic functions were preserved, and she never required inotropic support.

The patient initially presented with lymphopenia (0.63 G/L), but normal platelet count (429 G/L). The inflammatory syndrome was mild with a CRP level at 49 mg/L, and procalcitonin at 0.9 ng/mL. Initial ferritin dosage was at 530 µg/L. A systematic screening for cytokines levels was performed, and we found no proinflammatory cytokines

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Table 1: Biological findings. Inflammation and coagulation parameters, according to the time from onset of symptoms (days). We considered the first day of evolution as the day of onset (day 1: June 16th), the first day of sample was the day of transfer from Dakar to Paris, after 13 days of evolution (June 28th). The patient died seven days after ICU admission in our institution (19 days from onset date).

	D13	D14	D15	D16	D17	D18	D19
Serum creatinine (µM)							
Creatine Kinase (UI/L)	159	131	106	272	257	188	594
Lactate dehydrogenase (UI/L)	786	788	773	1182	1261	579	800
Ferritin (µg/L)	-	530	-	-	-	3590	1937
CRP (mg/L)	43	-	-	-	-	12	10
Procalcitonin (µg/L)	0.9	-	0.6	0.32	127	175	178
D-Dimers (ng/mL)	3126	3346	-	-	3701	-	-
Fibrinogen (g/L)	5.51	5.58	5.15	4.29	2.83	1.03	1.66
PT (sec)	20.5	18.7	20.1	25.9	59.8	68.8	20.3
APTT ratio	1.61	1.43	2	1.08	2.72	4.73	2.72
Anti-Xa activity (UI/L)	-	-	0.77	0.34	0.58	-	-
Fibrin monomers (µg/mL)	<7	-	-	79	149	35	-
vWF antigen (%)	-	680	-	-	-	1472	-
anti-PF4 IgG	-	-	-	-	-	Negative	-
Platelet count (G/L)	426	405	381	411	222	71	31
Lymphocytes (G/L)	1.96	0.63	0.92	1.06	2.09	1.39	1.04
Neutrophil count (G/L)	8.52	7.29	5.6	9.38	24.49	12.58	7.25
IL-6 (pg/mL)	-	22	-	-	-	135.4	-

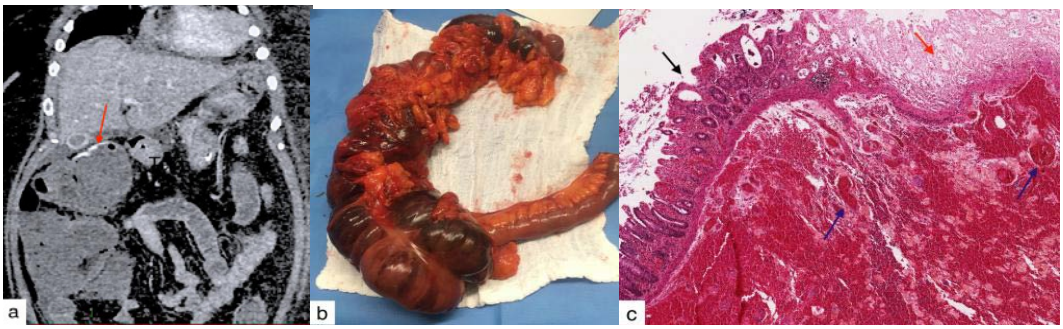

Figure 1: Right colic perforation due to mesenteric ischemia. Abdominal Computed Tomography in coronal view. (a): paralytic ileus with hydro-aeric levels and parietal pneumatosis. Red arrows indicate parietal bleeding, related to the beginning perforation of the right ascendant colon. Macroscopic view after right colectomy (b): Optic microscopy view of the colic mucosa: subnormal (black arrow) and ischemic (red arrow) epithelium, with small veins thrombotic occlusions (blue arrows) (c).

profile: TNF-α and IL-1β were undetectable (0 pg/mL), IL-6 and IL-10 were not increased (22 pg/mL and 8 pg/mL, respectively, data not shown). We found a prolonged activated Partial Thromboplastin Time (aPTT) at 39 seconds (ratio 1.43), a prolonged Prothrombin Time (PT) at 17.5 sec, normal FII, FV and FX, but decreased factor FVII (22%). Fibrinogen was increased at 5.58 g/L, D-dimers were initially at 3346 ng/mL and fibrin monomers negative (<7 µg/mL). Initial screening for lupus anticoagulant was positive, using the Dilute Russell's Viper Venom Time (DRVVT). Still, no Antiphospholipid (aPL) antibodies were found: Anticardiolipin (aCL) IgG <3 UC, IgM 2 UC (<20 UC), IgA 2 UC, anti-β2glycoprotein I (aB2GPI) IgG <7 UC, IgM 2 UC, IgA <4 UC, anti-Phoshatidylethanolamine (PE) IgG 4 U/mL, IgM 3 U/mL, anti-Phosphatidylserine/ Prothrombin (PS/PT) IgG < 9 U/ml, IgM <9 U/ml. The C3 complement was in the range at 0.95 g/L (0.8-1.7) Notably, SARS-CoV-2 shedding was still important with a cycle threshold of 24 in endotracheal secretions, but no virus could be detected in the serum. The serology was found positive with presence of IgM, and IgG anti-SARS-CoV-2 at a level of 7.76 (>1.68, data not shown).

She was placed under thromboprophylaxis since the beginning of her hospitalization in Dakar, with initial intravenous infusion of unfractionated heparin prior to her transfer to Paris, where prophylactic subcutaneous injections of low molecular weight enoxaparin at the recommended dose (4000 UI bid) were then preferred [5].

On July 1st, a plugged telescoping catheter of the respiratory tract was performed, and cultures were positive for *Klebsiella pneumonia,*

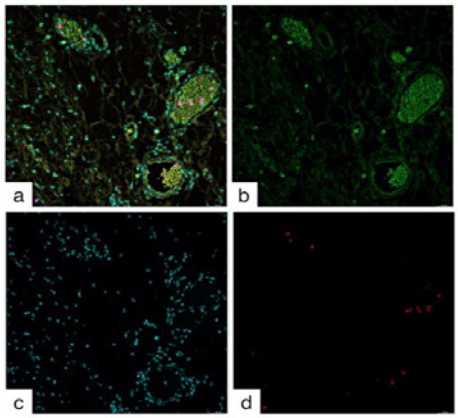

Figure 2: *In situ* immuno-fluorescence of the colic mucosa, showing microthrombi (a) Platelets assessed by CD42b (b) nuclei assessed by DAPI (c) Neutrophils assessed by MPO (d). (colic mucosa and deep veins with intraluminal clots, after surgery in a context of peritonitis). NETosis was assessed by immunofluorescence and measurement of circulating DNA-MPO complexes. We found normal expression of neutrophil activation markers, suggesting no involvement in thrombotic mechanisms.

Pseudomonas aeruginosa and *Enterococcus faecalis*. Simultaneous *Pseudomonas aeruginosa* bacteremia was found. She was treated with the association ceftazidime-avibactam and amikacin, and vasopressor support. Concomitantly, candidemia was also diagnosed and antifungal echinocandin therapy was initiated. Despite appropriate treatment, hemodynamic deterioration occurred 24 hours later, leading to multiorgan failure. Rapid assessment by echocardiography excluded the participation of a decreased cardiac output. An abdominal Computed Tomography (CT) confirmed mesenteric ischemia with right colitis, and the absence of macrothrombi in mesenteric vessels (Figure 1a). As expected, all inflammation

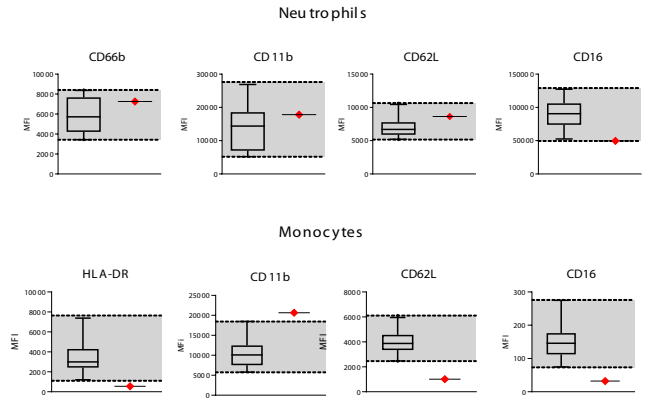

Figure 3: Immunophenotyping of circulating neutrophils and monocytes: Surface expression of main activation markers of neutrophils (top row) and monocytes (bottom row) in a cohort of 29 healthy volunteers (box plot) and for the case (red diamond). The gray zone between the dashed lines represent the range between the 5th and 95th percentiles of the values obtained on healthy volunteers. Data are Mean Fluorescent Intensities (MFI). Monocytes activation could be observed with downregulation of HLA-DR, CD62L and CD16, and upregulation of CD11b. Platelet-monocyte and neutrophil aggregates were not in the same range (24% and 16%, versus median [IQR] as those obtained from COVID-19 patients in our lab of 27% [11.5-58] and 12.5% [4.5-17.5], respectively). The downregulation of expression in monocyte HLA-DR suggests exhausted innate immune reaction, in line with normal cytokine dosage.

parameters increased markedly (Table 1). We observed an elevated procalcitonin at 10 ng/mL, and C-Reactive Protein (CRP) at 175 mg/L. IL-6 was increased up to 135.4 pg/mL, and ferritin 3591 µg/L. Platelet count dropped until 30 G/L, associated with hypofibrinogenemia, and increased fibrin monomers (Table 1), indicating Disseminated Intravascular Coagulation (DIC). Still, the same dose of enoxaparin was maintained. Indeed, heparin-induced thrombocytopenia was ruled out as anti-PF4 IgG were negative. Urgent laparotomy was decided on July 3rd, and a right colic perforation was found (Figure 1b). She died 12 hours later due to refractory shock.

Histopathological study found multiple venous thrombi, and ischemic damage in the colic mucosa, but neither sign of vasculitis, nor lymphocyte infiltration was seen (Figure 1c). No virus could be detected using *in situ* Polymerase Chain Reaction (PCR) on the bowel sample. *In situ* immunofluorescence showed a mild neutrophil infiltration (Figure 2). Neutrophils Extracellular Traps (NETs) measured by Myeloperoxidase (MPO)-DNA complexes were within normal range (9U/mL, N<19). In line with these findings, surface activation parameters of neutrophils (CD66b, CD11b, CD62L, CD16) were within normal range (Figure 3). Notably, von Willebrand Factor (vWF) antigen was measured at 680% at arrival in our ICU after thirteen days of disease evolution and increased to 1472% 3 days after, resulting from major endothelial activation. Important resistance to fibrinolysis was observed assessed by rt-PA modified Rotational Thromboelmastometry (ROTEM) assay (lysis time 6003sec versus a median [IQR] of 2609 sec [1855-3043] obtained from 26 COVID-19 patients) (Figure 4).

Discussion

Mesenteric ischemia has been described in COVID-19 patients [6] and could occur despite adequate anticoagulant therapy. Our case highlights that endothelial dysfunction exists specifically in the bowel where Sars-Cov2 proliferates. Surprisingly, although strong evidence support specific gut infection [7,8] *in situ* PCR was here negative. Severe endotheliitis reflected by elevated endothelial markers such as vWF might have driven the thrombotic disease in small veins of the bowel despite normal platelet-neutrophil interactions [9,10]. So far, the role of aPL antibodies in COVID-19 associated endothelial activation and thrombosis remains controversial [11,12]. aPL antibodies have been recently associated with neutrophil hyperactivity including the release of NETs [13], thus enhancing clot formations. However, in our case, only transient aPL antibodies in COVID-19 could be detected, contrasting with the negativity of all other immunological tests (anticardiolipin, anti-B2GPI, anti-PS/PT, anti-PE). Also NETs and markers of neutrophil activation remained in normal ranges, suggesting against this physiopathological mechanism. Notably, the altered fibrinolysis suggested by the thrombo-elastrogram profile is in line with endothelial dysfunction, and seemed to precede the development of peritonitis with DIC and multi-organ failure. We hereby suggest a closer monitoring strategy based on ROTEM to manage adequately anticoagulation [14,15] and to further guide new therapeutic approaches to help restore functional gut microcirculation.

In conclusion, this observation confirms that visceral complications might be originating from hypercoagulability leading to thrombosis in the microcirculation, and their frequency may be

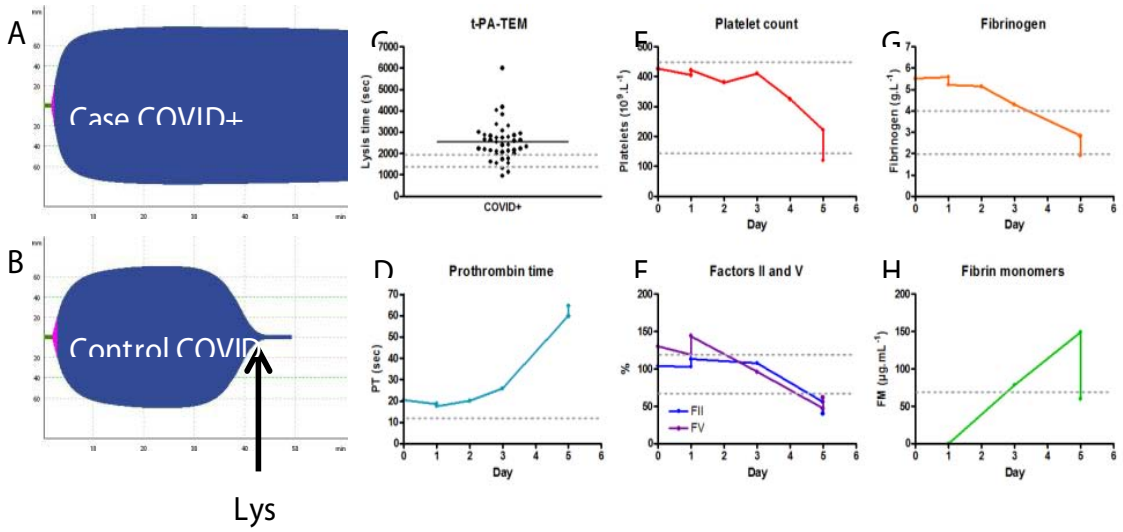

Figure 4: Biological characteristics. t-PA-modified thromboelastogram from the case (A) and from one representative panel of 40 other critically ill COVID-19 patients (B). Lysis time from the case compared to 40 COVID-19 ICU patients (C). The fibrinolysis alterations on the ROTEM are in line with endothelial activation markers such as markedly elevated vWF, which might have led to a thrombotic disease in small veins of the bowel, without vasculitis. (D-H) Dynamic profiles of PT (D), platelets (E), coagulations factors II and V (F), fibrinogen (G) and fibrin monomers (H). The horizontal lines show the normal limits of each parameter. The horizontal axis scale corresponds to the time from ICU admission (referral in Paris).

underestimated. Since this process might occur early in spite of well conducted anticoagulant therapy [6], relying on several coagulation parameters could help physicians to screen for at-risk patients, and improve the prognosis of SARS-Cov-2 in ICU.

Consent for Publication

The patient's relatives were informed and provided a written consent for this publication.

Authors' Contributions

PHW, DF, PRN, LD, NA and JFT were the main contributors to the redaction of the manuscript. DF, PRN, LD, IZ, NA analyzed the data. PHW, DF, PRN, NA, LD and JFT reviewed all the results and interpreted the data. PHW, JP and EDM were responsible for the clinical management of the patient. All the authors reviewed and approved the final version of the manuscript.

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