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Phlegmasia cerulea dolens superimposed on disseminated intravascular coagulation in COVID-19

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Abstract. COVID-19 infection has several cardiovascular implications, and coagulopathy is a common abnormality in these patients, often coupled with elevated plasma fibrinogen and D-dimer levels, contributing to adverse outcomes. Phlegmasia cerulea dolens (PCD) is a rare manifestation of deep vein thrombosis. It is life-threatening and can rapidly lead to venous gangrene of the extremity. Only a few cases of COVID-19 associated with PCD are reported in the literature, despite thromboembolism being the common paradigm between the two diseases. We present the case of a 64-year-old adult with acute severe COVID-19 pneumonia who developed PCD despite constantly elevated activated partial thromboplastin time and international normalized ratio. (www.actabiomedica.it)

Keywords: Phlegmasia cerulea dolens; disseminated intravascular coagulation; COVI-19.

Introduction

Coagulopathy is a common feature of coronavirus disease (COVID-19) (1) and contributes to adverse outcomes (2). Phlegmasia cerulea dolens (PCD) is a rare but life-threatening manifestation of deep vein thrombosis (3). Only a few cases of PCD associated with Covid-19 are reported in the literature, despite thromboembolism being the common paradigm between the two (4-6).

We present the case of a 64 years old man with severe COVID-19 pneumonia who developed PCD despite constantly elevated coagulation parameters.

Case Presentation

A 64-year-old man with a history of obesity (BMI 38 Kg/m^2), arterial hypertension, atrial fibrillation, type 2 diabetes, chronic kidney disease, obstructive sleep apnea, and chronic venous insufficiency presented to the Emergency Department complaining of dyspnea, fever, and chest pain which started 7 days before. The patient was hypoxemic in room air (SpO2 80% and PaO2 43 mmHg). Inferior limbs appeared normal. A molecular swab formalized diagnosis of SARS-CoV2-related pneumonia. Respiratory distress progressed despite non-invasive-ventilation and hemodynamic instability requiring vasoactive support ensued. The patient was intubated and transferred to the ICU. The patient received invasive protective ventilation and hemodynamic support with noradrenaline. Gas exchange progressively worsened to a PaO2/FiO2 ratio of 70 mmHg. He developed a shock, and his lower limbs started to appear mottled. Lung and cardiac ultrasound were compatible with severe interstitial pneumonia and with no signs of pressure overload of the right heart. His coagulation profile was highly altered, as both aPTT and INR were elevated (respectively 2.28 seconds and 6.42), platelets were 164,000/mm3, and D-dimer was 117,521 UI/ml. Coagulation parameters continually worsened (Table 1), and

Table 1. The daily progress of the patient's main laboratory tests. Note the ups and downs of the coagulation tests.

	07/01 h 06	08/01 h 06	08/01 h16	08/01 h18	09/01 h 01	09/01 h 05	10/01 h 06	10/01 h20	11/01 h 00	11/01 h 06	11/01 h 09	11/01 h 20	12/01 h 00	12/01 h 06	12/01 h 09	12/01 h 13	12/01 h 18	13/01 h 00	13/01 h 04	13/01 h 06	13/01 h 18	13/01 h 23	14/01 h 06	14/01 h 12	14/01 h14	15/01 h 00	15/01 h 06	15/01 h 12
WBC (/mm3)	14.23	7.69				12.70	10.64			9.56				14.02						18.95			20.95				20.91	
Hb (g/dL)	11.7	10.8				10	9.8			9.2				9.9						10.7			10.7				10.2	
CRP (mg/L)	327.38	334.77				221.80	100.1			54.69				55.94						87.97			132.82				330	
PCT (ng/mL)	2.83	4.84				5.05	3.92			2.26				1.28									1.61				248	
INR (sec)	6.42	6.81	8.29	9.86	6.7	5.92	1.52	1.85	1.87	2.02	2.10	2.36	2.46	2.59	2.77	2.91	3.25	3.56	3.79	3.47	3.16	2.95	2.88	nd	2.54	2.29	2.12	2.02
APTT (sec)	2.28	2.43	2.34	2.13	1.71	1.64	1.13	1.28	1.28	1.23	1.29	1.35	1.30	1.82	1.52	1.83	3.28	3.64	4.06	6.51	1.35	1.33	1.57	nd	1.55	2.06	248	2.02
PLT (/mm3)	164	114				150	142			137				163						188			213				111	
AT III	88%	85	83%	83%	76%		83%			78%				78%									107%		86%	80%	85%	
D-dimer (FEU ng/mL)	117521	113256	>140000	>140000	119509	113027	86975			46878										2657			5568		4913	3798	3683	
Fibr (mg/dL)	278	259	258	255	222		143			122				228						367			480		463	628	735	
Prot C				35%																								
Prot S				11%																								
Cr (mg/dL)	4.08	4.33	4.59			4.82	5.29			5.69				4.98						3.00			2.19				1.85	
NT-proBNP (pg/mL)	6194	7493				3219	2003							1426						1933			2992				6036	
HsTnI (ng/mL)	54.5	54.5				24.1	19																					

WBC: white blood cells; Hb: hemoglobin; CRP: C-reactive protein; PCT: procalcitonin; INR: International Normalized Ratio; aPTT: activated partial thromboplastin time; PLT: platelets; AT III: antithrombin III; Fibr: fibrinogen; Prot C: protein C; Prot S: protein S; Cr: creatinine; NT-proBNP: NT-proBrain Natriuretic Peptide; hsTnI: high sensitivity troponin I.

treatment with one unit of fresh frozen plasma and vitamin K was required. Inferior limbs' color progressively worsened, becoming frankly cyanotic, while pulses were still normal. Doppler ultrasound showed bilateral thrombosis of tibial and small saphenous veins. A continuous infusion of iloprost was started, as PCD was suspected (Figure 1). Continuous infusion of unfractionated heparin was instituted, at a dose of 500-1000 IU per hour, according to aPTT, as well as continuous veno-venous hemodiafiltration as the patient developed acute kidney injury. The patient's general conditions worsened (Figure 2), and despite maximal treatment, he passed away after eight days of ICU care.

Discussion

Although approximately 47% of COVID-19 patients have some form of thromboembolism, cases of PCD are poorly described in the literature (7,8). Only four other cases of PCD have been reported (4-6,9). In both COVID-19 and non-COVID-19 related PCD, the etiopathogenetic mechanism is an almost complete thrombotic occlusion of the venous outflow, which causes peripheral blood stagnation ischemia up to dry gangrene. The compartment syndrome that can develop, associated with the release of necrosis factors and cytokines, can lead to shock. Early signs include pain and edema, with a later progression to cyanosis, bullae, sensory and motor alterations, and finally, gangrene. PCD affects only one limb (usually the lower limbs), while both lower limbs' involvement is rare. PCD treatment should be particularly aggressive with pharmacological thrombolysis or surgical thrombectomy; anticoagulant therapy with intravenous heparin must always be guaranteed, with a target aPTT of 6 to 110 secs (3).

COVID-19 related PCD seems to differ from the classic form for at least a couple of reasons: often, PCD could be a manifestation of a wider alteration of coagulation (e.g., DIC), indicating a pro-hemorrhagic rather than a thrombophilic condition. DIC is constituted by abnormal activation of the coagulation and fibrinolysis processes that lead to diffuse microthrombi in the vascular tree, with consequently "consumption" of platelets and coagulation factors, and simultaneously release of fibrin degradation products and, in particular, of D-dimer. The plasma fibrinogen is, therefore, usually decreased more or less conspicuously. However, an increase in the plasma fibrinogen levels

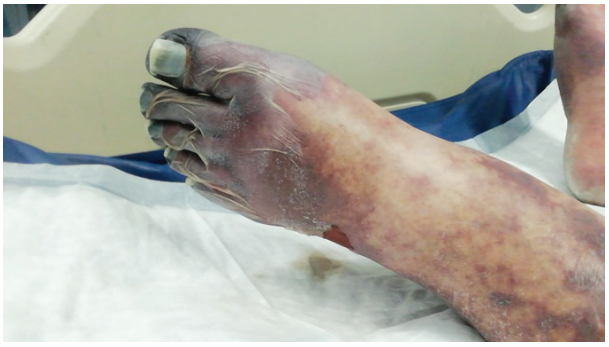

Figure 1. Image of phlegmasia cerulea dolens in the lower limbs in patients with COVID-19 related pneumonia.

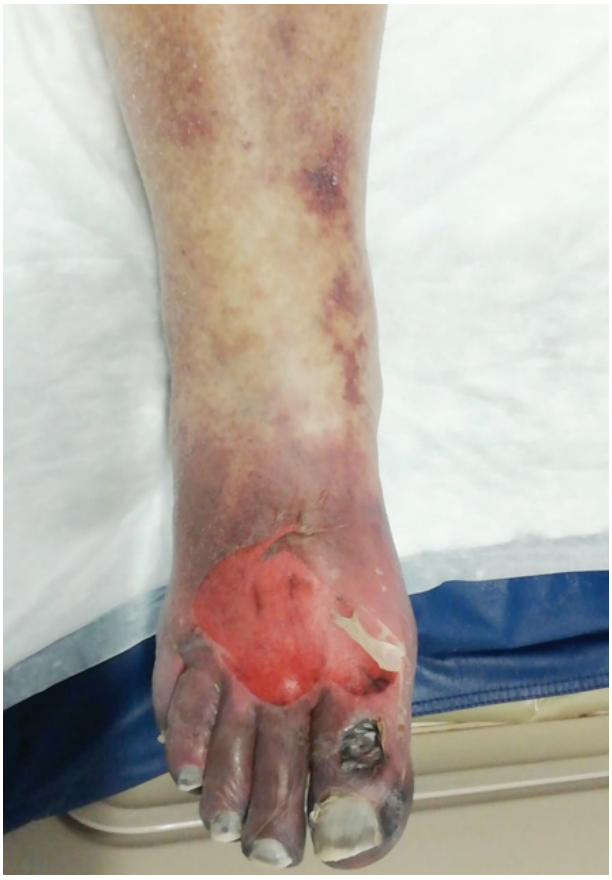

Figure 2. Image of phlegmasia cerulea dolens in the lower limbs in patients with COVID-19 related pneumonia (evolution).

was observed in COVID-19 patients. The upregulation of local fibrinolysis explains the mismatched D-dimer elevation in alveoli by urokinase-type plasminogen activator released from alveolar macrophages. The peculiar alterations of coagulation in COVID-19 patients have led some investigators to postulate the occurrence of a compensated DIC syndrome (10). In sepsis-related DIC, platelet count and PT prolongation correlate with disease severity and mortality.

In contrast, patients who die from COVID-19 usually show DIC signs with prolonged PT but with only mild thrombocytopenia, normal fibrinogen, and an elevated D-dimer. The latter has been repeatedly reported to be useful in monitoring COVID-19 severity and prediction of mortality. Although it is known that the etiological factors of DIC may be the neutrophil oxidative burst and the release of pro-inflammatory cytokines, the mechanism by which the SARS-CoV2 can develop this process is not yet known. Direct viral infection via the ACE-2 receptor of endothelial cells may play a role, as ACE-2 is involved in pathways regulating some of the endothelium's anticoagulant properties (10).

Different pathological entities can overlap each other: DIC, uraemic-hemolytic syndrome, hemophagocytic lymphohistiocytosis, antiphospholipid syndrome, and thrombotic thrombocytopenic purpura can contribute to the development of the so-called COVID-19 coagulopathy (10).

Our case is particularly instructive because it is the only one so far in which the development of PCD has occurred despite a spontaneous increase in coagulation times (i.e., supernormal INR and aPTT).

Conclusion

Clinicians should always have a high index of suspicion for thrombotic phenomena, up to PCD, even in the case of an alteration of the coagulation factors in a pro-hemorrhagic sense. For the prognostically negative significance of PCD itself, early diagnosis and aggressive treatment are essential to modify the prognosis.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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References

1. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020; 18:1743-1746.
2. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191:145-147.
3. Kou CJ, Batzlaff C, Bezzant ML, Sjulin T. Phlegmasia Cerulea Dolens: A Life-Threatening Manifestation of Deep Vein Thrombosis. Cureus 2020; 12:e8587.
4. Visveswaran GK, Morparia K, Narang S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Thrombosis: Phlegmasia Cerulea Dolens Presenting with Venous Gangrene in a Child. J Pediatr 2020; 226:281–284.e1.
5. Chun TT, Jimenez JC, Pantoja JL, Moriarty JM, Freeman S. Phlegmasia cerulea dolens associated with acute coronavirus disease 2019 pneumonia despite supratherapeutic warfarin anticoagulation. J Vasc Surg Cases Innov Tech 2020; 6:653-656.
6. Bamgboje A, Hong J, Mushiyev S, Pekler G. A 61-Year-Old Man with SARS-CoV-2 Infection and Venous Thrombosis Presenting with Painful Swelling and Gangrene of the Lower Limb Consistent with Phlegmasia Cerulea Dolens. Am J Case Rep 2020; 21:e928342.
7. Voicu S, Bonnin P, Stépanian A, et al. High Prevalence of Deep Vein Thrombosis in Mechanically Ventilated COVID-19 Patients. J Am Coll Cardiol 2020; 76:480-482.
8. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest 2020:S0012-3692(20)35146-1.
9. Morales MH, Leigh CL, Simon EL. COVID-19 infection with extensive thrombosis: A case of phlegmasia cerulea dolens. Am J Emerg Med 2020; 38:1978.e1-1978.e3.
10. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care 2020; 24:360.

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