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UNUSUAL PRESENTATION OF THROMBOEMBOLIC DISEASE IN A HOSPITALIZED PATIENT WITH COVID-19 INFECTION: A CASE REPORT

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Abstract

With no ideal specific therapy confirmed by the science community, and many low income countries barely being able to obtain a sufficient number of vaccines, as well as the long-term mental health impact, the COVID-19 infection makes for a worldwide health and global problem.

Case report

A COVID-19 positive patient was admitted due to poor condition, malaise and bilateral interstitial pneumonia with borderline oxygen saturation of 94%, hypoxemia with pO2 of 64mmHg, and elevated C reactive protein (CRP) of 70. The patient was put on oxygen support of 3l/min, and started parenteral antibiotic and LMWH in prophylactic doses - a combination that primarily improved the patient's condition. Three days after hospitalization marked shortness of breath with a drop in oxygen saturation of 62% referred. With further increasing of the oxygen flow, and a transfer to ICU, gas pressures showed significant worsening and the patient was put on mechanical support with a CPAP mask.

Despite adding pulsed doses of potent corticosteroid, rapid acting insulin for blood glucose control, and administerring convalescent plasma and parenteral nutrition, the CRP levels were increasing and oxygen was decreasing. Hypotensive, tachycardic and with reduced urine output, the patient was intubated and set up on IPPV mechanical support. Vasopressor stimulation didn't improve the diuresis and elevation of degradation products followed, as well as elevation of the troponin and cardiospecific enzymes - non of which was caused by sepsis.

Eight days after admission, the left arm presented as pale, cool and cyanotic. Fully deteriorated laboratory findings of multiple organ system failures (MOFS) were undoubtable; with the oxygen levels incompatible of life, and a CT scan with ARDS presentation, a continuous heparin infusion was the only solution. At the beginning, nothing indicated the deleterious outcome; however, with a highly unusual presentation of arterial thrombosis, the upper limb gangrene became too much and the patient died.

COVID-19 is primary a respiratory infection, but the virus can affect other organs and systems, with some very rare presentations and deleterious outcomes.

Keywords: COVID 19, limb ischemia, thromboembolism, COVID-19-associated coagulopathy, multiple organ system failure.

Introduction

The COVID-19 infection is a current and ongoing global pandemic, and the reason for this worldwide serious health issue that's further developing is the severe acute respiratory syndrome *Coronavirus 2* (SARS-CoV-2).

It was first reported in December 2019, in the Chinese province of Wuhan, which looks a long way from where we've come today. The cluster was initially reported on December 31, when the WHO China Country Office was informed. The Chinese authorities reported a new type of coronavirus (novel coronavirus, nCoV), first isolated on January 7, 2020 [1].

Most countries were not particularly worried, because in the first 45 days, just two countries outside of China were infected, and the assumption was that only those who had come into contact with the Wuhan seafood market, where the first case was thought to have occurred, had the highest probability of being infected [2]. It was, however, far from innocuous.

On January 23, 2020 the local governement put the city of Wuhan under lockdown. On January 30, 2020, The World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern, and later, on March 11, 2020 - a pandemic [3]. By March 13, 2020, the WHO deemed Europe the active center of the COVID-19 pandemic, witnessing the numbers of reported new cases of COVID-19 greater than those in China. By March 17, 2020, all European countries had a confirmed case of COVID-19 and more than 250 million people were in lockdown [4]. By May 22, 2020, the WHO said the epicenter had shifted to South America.

As of June 13, 2021, more than 175 million cases have been confirmed, with more than 3.79 million deaths attributed to COVID-19, making it one of the deadliest pandemics in history [3].

In The Republic of North Macedonia, the first case of a COVID-19 infection was detected in a woman who returned from Italy, at that time the European hotspot of COVID-19. It was the 26th of February when she came back and declared having had fever for about two weeks [5]. She was fully isolated and monitored in hospital for about 3 weeks, however, not one of her contacts developed any symptoms of a viral infection. The events that followed showed that there was much more that was unknown at the time.

After almost year and a half, we are confident that our knowledge has significantly improved. Having the typical pattern of airborne transmission like most of the other respiratory viruses, we now know that SARS CoV2 can spread by indirect contact with surfaces in the immediate environment, objects used by an infected person, as well as with close contact within 1 meter, when a droplet transmits from someone with respiratory symptoms while coughing or sneezing to an exposed person who is therefore at risk of having their mouth, nose or eyes open for potentially infective respiratory particles [6].

The symptomatology of COVID-19 patients varies: presentation has ranged from asymptomatic/ mild symptoms, to critical illness and mortality. Common symptoms include fever, cough and shortness of breath, elevated body temperature, from mild elevations to over 40C, and cough that is usually dry and irritative - but productive with sputum is not uncommon either. Other symptoms, such as malaise, fatigue, muscle and body aches, headache, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, loss of taste or smell, and respiratory distress can also be present.

With the mean incubation of 5.1, the majority of the patients have a mild presentation, with complaints on the most common respiratory symptoms; however, a significant number of patients experience serious symptoms and an unfavorable course; from severe respiratory distress, neurologic alterations, coagulation disorders to multi-organ failure disease, hyper-inflammatory syndrome and death [7]. Clinical presentation may overlap and vary, and a patient's clinical status may change over time. Oxygen saturation (SpO_2) on room air at sea level, respiratory rate, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen, distribution and extensity of lung infiltrates are among those who can alarm that the patient's clinical status is taking an unfavorable course [8].

Clinical trials suggest that severe COVID-19 course and greater mortality was more often seen in males, older individuals, individuals in poverty, black persons, and patients with diabetes and severe asthma as comorbidities. A European multicenter observational cohort study found frailty to be a greater predictor of mortality than age or comorbidities [9-10].

As when first presented, the challenge was the detection of the virus, managing contacts, social isolation, and searching for a focused treatment. After a year and a half, the improvement of the treatment, post-Covid complications and vaccinations are the main target. Many drugs had their chance during this past year; from antimalarics and antiretroviral lopinavir/ ritonavir combination, to favipiravir, ivermectin and interleukin inhibitors. The U.S. Food and Drug Administration has only approved the antiviral drug remdesivir for hospital COVID-19 treatment in patients aged 12 and older, and authorized baricitinib, monoclonal antibody treatments and convalescent plasma immune based therapy among others for emergency use during this public health emergency. In addition, many more therapies are being tested in

clinical trials, and until then, many non-specific immune modulating treatments like corticosteroids and supplements are largely in use [15-16,8].

And while hospitals continue to fight with the challenges of acute COVID-19, a new Covid-19 derived syndrome, labelled as either post-COVID, or long-COVID syndrome takes the spotlight[11].

With speculative findings as to whether it is a singular disease process, the CDC recently proposed defining post-COVID as sequelae that extend more than 4 weeks after the initial infection, in which recovering SARS-CoV-2 patients suffer from persistent and, often, debilitating symptoms extending to several months after [11].

Either "post-acute sequelae of COVID-19" (PASC) or multisystem inflammatory syndrome in adults (MIS-A), even people who did not have symptoms can have post-COVID conditions [8].

The exact mechanism is still not well defined; it varies from low antibody response to a SARS-CoV-2 infection and prolonged inflammatory response, to de-conditioning and possible re-infection marked symptoms. From non-specific symptoms such as fatigue, muscle aches and pains, poor sleep, cough, breathlessness, night sweats, and poor temperature control, to more specific organ-related symptoms, such as orthopnea and exercise intolerance, chest pain, palpitations, headache, brain fog, depression and anxiety - poor quality of life can be referred for many months after [13-14].

Conclusively, what can be done to fix this? Fair politics of distribution to safe and effective vaccines is critical for ending the COVID-19 pandemic, so it is hugely encouraging to see so many vaccines taking their best. As of June 3, 2021, the WHO has evaluated that Astra Zeneca/Oxford, Johnson and Johnson, Moderna, Pfizer/BionTech, Sinopharm and Sinovac vaccines have met the necessary criteria for safety and efficacy.

Although no vaccine is 100% protective, they prevent people from getting seriously ill or die. But it's not vaccines that will stop the pandemic, it's *vaccination*; by June 20, over 2 412 226 750 people have been vaccinated. We must ensure fair and equal access to vaccines, and tend to the opportunity that every country can fully protect their people, starting with the most vulnerable. Safe and effective vaccines are the only tool at our disposal: but for now, wearing masks, cleaning hands, ensuring good ventilation indoors, physically distancing and avoiding crowds remains imperative and what we must do [17].

Case report

Five days after reporting the first symptoms, a woman aged 68 was presented for examination with complaints of dry cough, malaise, loss of appetite, and a dry mouth. She didn't have any high temperature, but her blood pressure was difficult to control in those days, although she was on her regular therapy with medication prescribed by her doctor several years before. She was first examined by her family doctor and with the diagnostic suspicion of a possible SARS CoV2 infection, she was tested one day before hospitalization. The test was positive.

The woman started using ivermectin, an antiparasitic drug potentially useful in Covid-19 treatment, at that time largely used in North Macedonia - 21 mg o.d. according to her body mass.

The next day she was referred for a check-up at the triage center of the City General Hospital *8th September*, at that time serving as the country's COVID-19 center. A detailed physical examination was performed; Laboratory and vital signs followed (Table 1).

The electrocardiogram revealed sinus rhythm, normal axis, no changes in morphology and conductivity, no signs of acute cardiac presentations. Auscultations of the lungs showed pulmonary vesicular breathing, with prolonged expiration and weak breathing sounds in the middle and basal right parts of the lungs, as well as the basal left parts. Crackles were also present at the basal parts of the lungs, both sides.

Chest X-ray was also obtained: Figure 1 demonstrates multifocal opacities in the middle and basal parts of the right lung, with peripheral distribution, also areas of consolidation in the basal left part too.

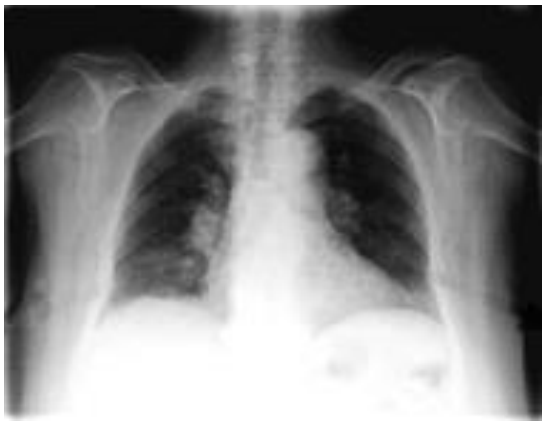

Figure 1. X-Ray demonstrating bilateral lung consolidation

The patient was admitted to the Department for infectious diseases, set to oxygen support with an oxygen mask with 3l/min flow, with a good SpO2 improvement to 97%. The blood pressure normalized with the home prescribed medications bisoprolol 2,5mg and lisinopril 5mg. Antibiotic therapy with parenteral Ceftriaxone 2g was started; fluid replacement with balanced crystalloids, gastroprotection with histamine H2 receptor antagonist - famotidine, LMWH Fraxiparine 0,4IE s.c/o.d, and her standard therapy for hypothyreosis – levothyroxine 50mg 0.d. was included.

On the second day of hospitalization the patient felt better. Gas analyses were improving, the appetite was better, the blood pressure was controlled.

On the eighth day of the symptoms onset, and the third day of hospital admission, the woman complained on shortness of breath. She started to feel the oxygen support as insufficient, the cough was worsening, she couldn't finish a sentence without a need for rest. SpO2 dropped to 62% and it did not improve with the elevating oxygen flow rate. She was started on a potent corticosteroid – metilprednisolone 2mg/kg/per day b.i.d. and was a candidate for receiving a convalescent plasma.

New laboratory tests followed (Table 1) and the patient was transferred to the ICU. Mechanical support with a continuous positive airway pressure (CPAP) mask was set, a second antibiotic was introduced - fourth generation fluoroquinolone moxifloxacin 400mg o.d. plus to ceftriaxone; blood glucose levels were corrected with rapid acting insulin - novorapid. Central line, urine output and further ICU monitoring was performed, initial SOFA score was 9. The convalescent plasma also was administered, parenteral nutrition followed, patient started to use the prone position with good tolerance and good results.

In the following two days there was a slight improvement in the overall condition. Five days after admission, her condition rapidly worsened. She felt extremely dyspnoic, fighting for every breath, the oxygen saturation decreased to 50% on a CPAP mask, she was tachycardic, hypotensive, with a urine output of 500ml for 8h. The CPR team performed tracheal intubation, and the patient was put on a mechanical ventilation with intermittent positive pressure ventilation (IPPV). Ceftriaxon was replaced with meropenem 1,0g t.i.d, and fluconasol was also administrated - 200mg.

The next day, her vital signs started to deteriorate. She was hypotensive, with a low urine output: only 20ml/h, a SpO2 of 86%, and a body temperature of 37,8C. Vasopressor stimulation with catheholaminergic dopamine started, with 4mcg/kg/min continuous IV infusion, with improvement in the blood pressure to 130/70mmHg, and diuresis of 1200ml/per day.

On the seventh day of hospitalization, some unexpected laboratory changes happened. CK, CKMB and troponin increased, and the D-dimer levels were markedly elevated to 10200. The patient was sedated, so she could not report any chest pain, but controlled ECG showed nonspecific changes, sinus rhythm with flattened T waves in leads II, III, aVF, V4-V6. Echocardiography was performed with heart chambers within the normal ranges, and ejection fraction of 50%, no wall motion abnormalities, no masses in the chambers, no PFO. Heart team adjusted the therapy: ASA 100mg o.d, clopidogrel 75mg o.d, fraxiparin 0,6IE 2x1 s.c. and atorvastatin 40mg o.d. were added.

Table 1. Laboratory findings at initial diagnosis (day 1) and during hospitalization (day 3, day 5, day 7 and day 9)

	Day 1	Day 3 CPAP-MV	Day 5 IPPV-MV	Day 7	Day 9		Normal range
W	4,	10,0	15,4	17	11,		3,5-10
Gr	78	88,9	89,2	89	90,		35-80
Lv	16	7.7	7.0	6.	5.4		15-50
Plt	96	160	120	19	57		100-400
Hg	13	130	126	10	109		115-180
Na/	14	144/4,1	145/6,1	14	149		136/145; 3,5-
bili	8,	10	10	12	8		5-21
ure	7.	12.6	14	25	40		2.8-7.2
kre	73	110	150	21	450		49-115
CK	21	125/18	159/24	89	392		10-170; 7-30
tro	ne	<0.01	0.03	18	3.1		<0.01
glu	8.	14.0	18.3	16	16		4.1-5.9
Ast	35		30/	25	420		5-37; 10-63
alb	36		30,4		28		35-52
LD	30	471	500	45	168		81-234
ddi	53	440	1000	10	350		<500
PT	10	10,9	11,2	13	13,		11-13,5
AP	31	28,2	36,4	39	45		26-34
feri	80	990			952		20-260
IL-	43	29,7			227		<2
CR	70	91,9	84,2	65	104		<10
Pro	0.		0.01		0.0		<0.5
TA	16	135/70	100/70	90	80/		
HR	90	100/min	140/min	10	60/		60-100
Sp	92	62-90	50-85	86	80		>96
diu	30	3400	500ml/8h	20	100		0.5-
bo	36		37C	37	35,		36,5-37,4
pH	7,	7,44	7,37	7,	7,2		7,35-7,45
pO	72	65	77	62	53		90-100
pC	36	36	35	50	65		34-40
BE	0,	2	2,4	4,	-		-2/+2
lact	0,	1,2	2,4		8,0		0,5-2,2

The following day, the patient presented with cool, pale and livid-cyanotic left hand and forearm. Pulse on the distal a.radialis and a.ulnaris was not present, bedside vascular ultrasound showed absence of the signal below distal a.brachialis. Detailed estimation of the patient overall position was under observation: still hypotensive on dopamine stimulation, hypothermic, oliguric, with lung CT showing massive lung ground glass opacities with peripheral distribution and signs indicating ARDS, gas analyses with respiratory acidosis and worsened kidney function. CT angiography was not performed, but the diagnose of upper limb ischaemia was obvious.

The patient's ICU team decided that patient's condition was very poor, so they started a continuous heparin infusion with a dose of 18U/kg/h and vasopressor Noradrenaline in 0,5 microg/kg/min.

The following day, the left arm was paler and livid in the upper parts, and the fingers were gangrenous. Heparin dosage was corrected to 20U/kg/h, because of insufficient aPTT.

However, late in the evening, sharp deterioration of the condition proceeded; with a heart rate of 30/min, blood pressure 70/40mmHg, SpO2 35%, approached resuscitation was unsuccessful and the patient died.

Discussion

Even after year and a half, the COVID-19 pandemic is still increasing with all its mutations and variants. With more than 178 million cases confirmed and 3 884 000 deaths by the time this article is published, it has been one of the deadliest pandemics in history [4]. More than 95% of the people who contract COVID-19 recover, at least a third do not develop noticeable symptoms. Of those people who develop symptoms, most (81%) have a mild to moderate presentation (up to mild pneumonia), 14% develop severe symptoms (dyspnea, hypoxia, more than 50% lung involvement on imaging), and 5% suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction). People at the greatest risk of mortality from COVID-19 tend to be those with underlying conditions, weakened immune system, serious heart or lung problems, severe obesity, or aged over 65 [18].

With the lungs being the organs most affected by COVID-19, attacking the host cells via the receptor for the enzyme angiotensin-converting enzyme 2 (ACE2), autopsies of people who died of COVID-19 found diffuse alveolar damage, with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation, pulmonary edema and interstitial mononuclear containing inflammatory infiltrates, dominated by lymphocytes as a pathological finding. Acute myocardial injury and chronic damage to the cardiovascular system are also seen frequently. An acute cardiac injury was found in 12% of infected people admitted to the hospital in Wuhan, China, and is more frequent in the severe forms of the disease [48]. Another common cause of death is kidney failure, with reports showing up to 30% of hospitalized patients both in China and in New York have experienced some injury, including patients with no previous kidney problems.

Some very rare presentations of respiratory virus complications are high incidence of thrombotic events, venous thromboembolism as well as ischaemic events. Most prevalent in the ICU COVID-19 patients, they are related with high mortality and poor prognosis. Every organ and system can become victim of the virus [18].

The aforementioned case report is something not frequently seen. The patient's unfavorable outcome was inevitable, but an upper limb ischaemic event was something that could in no way be predicted. With no previous anamnesis of blood and haemostatis system disorders, and normal parameters at hospital admission, gangrene was not at all an option for this patient. With incidence of <5% in some studies,[19] upper limb ischaemia is a relatively uncommon clinical syndrome that mainly affects elderly patients with cardiovascular comorbidities.

Arterial thromboembolism represents the most common cause with a cardiac thrombus being the source, and the most common site the brachial artery. Two-thirds of the patients had coexisting atrial fibrillation, 84% also had associated ischemic heart disease or a recent myocardial infarction [20]. The presence of severe comorbidities not only affects incidence, but also increases the risk of many revascularization interventions. Thus, conservative therapy has significant benefits in terms of morbidity and mortality in a high-risk patient population, as surgical options can be reserved in failed conservative therapy and hence reduce potential operative complications in a generally elderly and comorbid population [21].

Coagulation abnormalities in Covid-19

Significant coagulopathy and hypercoagulability is one of the major hallmarks of the COVID-19 course, manifesting as venous and arterial thromboembolism along with cardiovascular and lung failure. Incidence of thromboembolic disease is reported to be high in SARS-CoV2 disease cases and is seen in a multitude of organ systems ranging from cutaneous thrombosis to pulmonary embolism, stroke or coronary thrombosis, sometimes with catastrophic outcomes [22].

The presence of hypercoagulation and thromboembolic complications have been noted to correlate with a more severe course of the disease involving the need for admission into ICU and potentially, death [26]. With pulmonary embolism as the most reported VTE manifestation, arterial microthrombosis has become more evident representing cerebral, coronary, extremity and visceral arteries ischaemia as most prevalent. In some observational series, thrombotic complications have been noted to be as high as 31% in patients requiring ICU admission and the risk persists even in patients on anticoagulation. Approximately

20–55% of patients with a COVID-19 infection develop coagulation abnormalities, which correlate with the severity of their infection and are associated with higher mortality [25].

Patients with COVID-19 coagulopathy have a tendency to develop both arterial and venous thromboembolic events more than bleeding. There is little knowledge so far on the optimal management of these patients, as COVID-19-related coagulopathy appears to have distinct clinicopathological features, different from other systemic coagulopathies associated with severe infection. A recent autopsy study found that almost no organ in the body is spared of thrombosis [26].

Evidence points towards a key role of endothelial disfunction, hypercoagulability, hypoxia, coagulation dysfunction and inflammation with overproduction of proinflammatory cytokines mimicking a "cytokine storm" contributing to thrombosis. The pivotal role of thrombo-inflammation and endothelial injury in the pathogenesis of the disease is being increasingly recognized [24].

Overproduction of pro-inflammatory cytokines, IL-2, IL-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A, including tumor necrosis factor (TNF), Interleukin 6, IL-8, and IL-1β, is believed to be the cause of what is being termed, "cytokine release syndrome" or "cytokine storm", a phenomenon which is however not unique to this disease and has been noted in sepsis and sterile inflammation as well. This exaggerated cytokine response may lead to multiorgan failure and eventually death. IL-6 levels may correlate with disease severity and a procoagulant profile [33].

In addition to elevations in pro-inflammatory markers, hypercoagulability has been identified to be playing a key role in determining a prognosis in patients with COVID-19 leading to multiorgan failure. It has also been speculated that direct viral infection of endothelial cells through the angiotensin-converting enzyme 2 receptor may be the cause of arterial thrombosis in patients with COVID-19. Probably, a combination of more mechanisms, but not one, is responsible for the increased rate of thromboembolic events in COVID-19 patients [26,35].

Recently, there is evidence of complement activation in COVID-19 by direct endothelial infection which includes a release of anaphylotoxin C5a. Complement activation not only drives neutrophil dysfunction leading to susceptibility to secondary infections, but also activates the coagulation system leading to diffuse thrombotic microangiopathy and end-organ dysfunction.

Two parallel activation cascades are enrolling when endothelial insult takes place; the inflammatory pathway releases cytokines, and the activation of a microthrombotic pathway is mediated by release of Von Willebrand factors (VWF) enhancing platelet activation and consumption thrombocytopenia, elevating the factor VIII. But in contrast to the typical consumptive coagulopathy and disseminated intravascular coagulation (DIC) observed in sepsis, patients with COVID-19 typically have a relatively normal coagulation and platelet profiles. Progression to DIC occurs in a minority of patients. Therefore, keeping the Virchow's triad, thrombosis is driven both by the activation of coagulation factors and endothelium, and in-situ immune-thrombosis as a mechanism explaining the micro and macro-thrombotic manifestations of the disease [28,31].

Reports of elevated d-dimer levels and fibrinogen are increasingly prevalent in COVID-19 affected patients; they tend to correlate with increased levels of inflammatory markers and may be indicators for disease severity in addition to thrombotic risk [22,29]. Han and colleagues described changes in blood coagulation during severe SARS-CoV2 infections with increased values of D-dimer, fibrin or fibrinogen degradation products, fibrinogen; decreased anti-thrombin values, prothrombin time activity, and thrombin time [46].

D-dimer levels at the time of hospital admission is a predictor of the risk of development of acute respiratory distress syndrome (ARDS) and requiring mechanical ventilation, the risk of ICU admission and the risk of in-hospital mortality and death [28,33]. Recently, Tang et al.[8] assessed 183 patients with COVID-19, with notable differences between patients who died and those who survived; D-dimer and fibrin degradation products were markedly increased and PT prolongation was also evident in those who passed away. Other hemostatic abnormalities like increased coagulation factors, decreased levels of protein C, protein S, antithrombin, hyperactivation of platelets and neutrophils, and acquired antiphospholipid antibodies are also observed [35].

Nevertheless, it is yet unknown whether these hemostatic changes are specific for SARS-CoV2, or if they are a consequence of a cytokine storm that precipitates the onset of SIRS, as observed in other viral diseases. Recent studies report ischaemic presentations in patients with severe COVID-19 in the setting of elevated antiphospholipid antibodies. Whether antiphospholipid antibodies play a major role in pathophysiology of thrombosis associated with COVID-19 requires further investigation [33-34].

In order to control the attendant prothrombotic state associated with COVID-19, the International Society of Thrombosis and Hemostasis (ISTH) reveal guidance recommending that in the absence of contraindications, "prophylactic dose low molecular weight heparin (LMWH) should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection". In a similar manner, the American Society of Hematology also recommends that "all hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux, unless they are judged to be at increased bleeding risk" [26].

Whether the full-dose blood thinners decrease the need for life support and improve outcome in hospitalized COVID-19 patients requires further investigation [27,30,32].

Acute limb ischaemia

Incidence of acute limb ischaemia (ALI) has tremendously increased in the Covid-19 area; its incidence started to present as high as 16% in some studies. Bellosta et al. reported that the number of patients presenting with ALI has significantly increased in 2020 compared with the same period in 2019 which may be considered as a sign of ALI related with Covid-19. Although rare when compared with venous thromboembolic events in Covid-19, ischemic events were mostly observed in ICU patients [36]. The presence of traditional cardiovascular risk factors for atherosclerosis in patients who develop ALI is seen in Covid-19 patients as in the rest of the population. Al-Zoubi et al. report that patients who developed ALI during hospitalization had similarities.

All of them males, with COVID-19 related pneumonia, were managed in the critical care units, and had the traditional cardiovascular risk factors. Finally they were all unfit for revascularization surgery and died within 24 hours of the ALI diagnosis [34]. Results from autopsy studies in patients who died from a COVID-19 infection revealed the presence of generalized thrombotic microangiopathy mainly affecting elderly male individuals with obesity and cardiovascular comorbidities [42]. Woehl et al. in their study also underline the fact that patients predisposed to endothelial lesions (hypertension, male sex, smoking, diabetes, coronary artery disease) could be more prone to infection of the endothelium induced by the virus, with endothelitis being responsible for thrombosis formation [45].

However, ALI can develop in those without typical risk factors for thrombosis. None of four patients in one review had any history of thromboembolism or risk factors that could justify their ischemia [40]. While ALI is a complication of hospitalized patients with severe COVID-19, it can also occur in patients with mild symptoms, even in patient with an absence of significant respiratory symptoms [43]. Arterial events presenting as acute limb ischemia have also been reported in younger patients with no comorbidities and while receiving a prophylactic dose of LMWH [42]. Diagnosis of ALI in critically ill patients is also challenging. In a review of a small cohort of 16 patients with acute upper or lower extremity ischemia, only 8 underwent confirmatory imaging studies. The patient's overall stability, degree of ischemia, and limb viability are crucial in determination to whether intervention is appropriate, considering the severity of the systemic illness. Similar to damage control in trauma patients, the principle of "life over limb" is justified. Based on published case series, less than half of the patients with COVID-19 associated ALI underwent procedures for limb salvage with mortality rates as high as 50% and risk of death nearly three-fold higher in patients with arterial thrombotic events [37,47].

Even if revascularization is applicable, successful rates were disappointingly low in patients with COVID-19 when compared with previously reported series. Authors argue that this lower-than-expected success rate was due to a COVID-19-related hypercoagulable state [39]. Findings of a "desert foot" situation and a typical absence of the forefoot microcirculation despite the removal of the thrombus in ALI and aspect of early recurrent thrombosis after treatment, confirm the observation that a suspect marked hypercoagulability might be a contributory cause of technical failure [36,41].

In this context, de Roquetaillade et al. reported in their study that all of the affected patients at the time of the ischaemic arterial event were on anticoagulant treatment: 50% with a thromboprophylaxis dose and 50% received full-dose anticoagulation [43]. This challenges the audium to further investigate optimal anticoagulant management strategies in COVID-19 patients, both for prophylaxis, and with therapeutic purposes.

Conclusion

Covid-19 is primarily a respiratory infection, but the virus can affect other organs and systems, with some very rare presentations and deleterious outcomes. Acute thrombotic events are a serious and potentially life-threatening complication in patients with COVID-19. ALI incidence is increasing in COVID-19 patients and its management might be harder than expected, due to the the patients' overall situation. Further studies are needed to determine the relationship between COVID-19 infection and ALI.

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