Peripheral artery disease, the 'lost syndrome' during lockdown for COVID-19: A report of three cases

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Abstract. The recent coronavirus disease 2019 (COVID-19) pandemic has significantly increased the burden placed on healthcare systems worldwide. This health emergency has led to changes being implemented in the organization of health institutions and has shifted the focus on pandemic management. This has led to marked changes being made in the treatment of patients without COVID-19, and has resulted in more difficult access to healthcare, with ensuing delays in diagnosis and treatment. Vascular diseases, including peripheral artery disease (PAD), require prompt treatment in the majority of cases in order to save affected limbs. Moreover, COVID-19 may result in acute arterial and venous complications, which need to be promptly recognized and treated. The present study describes three paradigmatic clinical cases of hospitalized patients, which are representative of the different forms of the 'lost syndrome' caused by either the direct effect of COVID-19 or by the effects of COVID-19 on the healthcare system and lifestyle factors. Prophylaxis against arterial and venous thrombotic events is crucial in patients with COVID-19, particularly those with a marked inflammatory state. On the other hand, the COVID-19 pandemic has diminished the access to healthcare system for patients with other chronic pathologies, with potential severe consequences for vulnerable patient groups, such as those with PAD and cardiovascular diseases. For these patients, the authors' experience over the last few months suggests that more suitable measures need to be adopted to avoid additional severe consequences on public health. In addition, it is necessary to identify pathways that will allow these patients to have rapid access to treatment with marked improvements in outcome.

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Introduction

In December 2019, a new cluster of pneumonia was reported in Wuhan, China, which was linked to a novel coronavirus on January 7, 2020 (1). On January 30, the World Health Organization declared an international public health emergency (2). Coronavirus SARS-CoV-2 syndrome spread rapidly and, due to the increasing number of infections and hospital admissions, there was a shift from the provision of regular healthcare towards the provision of urgent services alone. The number of physical examinations was significantly reduced, which may have delayed the diagnosis and treatment of patients with peripheral artery disease (PAD), both with and without coronavirus disease 2019 (COVID-19) (3).

In these cases, the excessive delay in access to the healthcare system or a loss of regular follow-up altered the course of PAD, with severe implications for the affected patients. Therefore, the impact of the global pandemic emergency includes the effects of untreated PAD and the development of what may be referred to as the 'lost syndrome'. The present study describes three paradigmatic clinical cases and examines the negative impact of the lockdown period for COVID-19 on patients with PAD.

Case reports

The present study describes three clinical cases of patients admitted to the Angiology Unit of San Giacomo Hospital of Castelfranco Veneto (Castelfranco Veneto, Italy), which are considered as representative of the different forms of the 'lost syndrome', caused by the direct effects of COVID-19, or by the effects of COVID-19 on the healthcare system and lifestyle factors.

The first case is an example of acute arterial and venous thrombosis, a complication developed during COVID-19 infection. The second case is an example of a delayed diagnosis due to the reluctance of the patient to visit the hospital due to a fear of contracting SARS-CoV-2 and, consequently, late admission to the hospital. The last case represents the negative effect of the lockdown period on therapeutic lifestyle modifications, such as physical activity, which are a cornerstone in the treatment of patients with PAD. Written informed consent was obtained from the three patients whose cases are presented herein.

Case 1. A 67-year-old male was admitted to the Emergency Department of San Giacomo Hospital for respiratory failure. SARS-CoV-2 RNA was detected in the nasopharyngeal swab. The patient was a former smoker and had type 2 diabetes mellitus, for which he received oral anti-diabetic drugs. Moreover, the patient had undergone gastric resection for ulcer and cholecystectomy 30 years prior. The patient was transferred to a COVID-19-associated hospital and received treatment with oxygen using a high-flow nasal cannula, systemic steroid therapy and intravenous antibiotics. While the lung disease appeared to improve, the patient developed sudden acute pain on his left leg, with pallor and paresthesia, suggesting acute limb ischemia. Computed tomography angiography revealed the thrombotic occlusion of the tibioperoneal trunk and the anterior and posterior tibial arteries of the left lower extremity. The patient was transferred to the Department of Vascular Surgery of San Giacomo Hospital and underwent urgent surgical selective thrombectomy of the tibioperoneal trunk, and the anterior and posterior tibial arteries. Lower limb salvage was successful, and duplex ultrasound (DUS) performed immediately following the procedure revealed the patency of the treated arterial vessels and the presence of bilateral deep vein thrombosis (DVT) in the soleal veins. The patient was initially treated with low-molecular-weight heparin (LMWH), and this was then changed to a direct oral anticoagulant (DOAC). The arterial DUS performed at 1 month following the vascular procedure confirmed the patency of the revascularized vessels. A cardiac evaluation with echocardiography and Doppler ultrasound revealed normal heart function and a 24-h Holter electrocardiogram excluded the presence of arrhythmias. Glycemic control was satisfactory with basal-bolus insulin therapy. The laboratory tests revealed low-density lipoprotein cholesterol levels of 140 mg/dl, and atorvastatin was increased from 20 to 40 mg daily and combined with ezetimibe. The patient was discharged with the following therapy: Aspirin, DOAC, metformin, steroid, atorvastatin and ezetimibe.

Case 2. An 86-year-old female was hospitalized at the Angiology Unit of San Giacomo Hospital for pain, pallor and pulselessness of the lower extremities, suggesting acute bilateral leg ischemia (Figs. 1 and 2). DUS of the lower limbs revealed the presence of bilateral extensive thrombi of the popliteal arteries below the knee. Bilateral DVT was also detected, proximal in the left thigh and distal in the right calf. The symptoms had first appeared almost 10 days earlier. The patient resided alone and, due to the pandemic, did not have regular contact with her relatives. Moreover, she underestimated the symptoms due to a fear of being administered to the hospital. All these circumstances contributed to the advanced and severe clinical presentation when the patient arrived at the hospital. The patient's medical history included locally advanced colorectal cancer, treated with surgical resection and ileostomy 4 months earlier, hypertension and hypertensive cardiomyopathy, dyslipidemia, carotid vascular disease (moderate stenosis of the internal carotid arteries) and previous surgical repair of an abdominal aortic aneurysm. The laboratory tests revealed a pattern of intravascular disseminated coagulation. The COVID-19 test was negative. Given the poor overall condition of the patient, she was treated with anticoagulants, antibiotics and morphine to control the pain. The patient was stabilized from a hemodynamic point of view and discharged at home with palliative care. She succumbed to her condition 3 weeks later.

Case 3. A 60-year-old male affected by PAD and followed-up in the Angiology Unit of San Giacomo Hospital was previously treated with percutaneous transluminal angioplasty of the right femoral artery for acute limb ischemia 7 years prior. The patient had since maintained satisfactory physical activity (1 h of walking per day) and had not complained of claudication during the follow-up period. His medical history also included hypertension and dyslipidemia. During the lockdown period, the patient markedly reduced his physical activity and his usual walking exercise. After 6 months, he reported a worsening of his mobility, with the appearance of right leg pain following a 200-m walk at a fast pace and a 1-km walk at a slow pace, instead of his usual 5-10-km walk. The DUS and ankle-brachial index (ABI) results were unaltered as compared to the previous examination. However, the patient noted a worsening of his functional capacity, which adversely affected his quality of life. The COVID-19 test result was negative. The patient remained on medical therapy with antiplatelet, lipid-lowering and anti-hypertensive drugs and was encouraged to return to his former levels of physical activity.

Discussion

Coronavirus SARS-CoV-2 appears to generate an inflammatory state, characterized by a 'cytokine storm', which induces vascular inflammation and potential endothelial involvement (4). This inflammatory state can contribute to the development of cardiovascular complications and thus, to the worsening of pre-existing vascular diseases (VDs) (5). Due to a global inflammatory response and endothelial cell damage, COVID-19 may cause coagulation disorders, which may lead to severe venous and arterial thrombotic events (4). As regards the pathophysiology of COVID-19 and its complications, Huang *et al* (6) described that both intensive care unit (ICU) and non-ICU patients exhibited a vast array of plasma inflammatory biomarkers, including interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon inducible protein, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α and TNF-α, compared with healthy adults.

The clinical presentation and evolution of the first presented case suggested potential vascular complications of COVID-19. Inflammatory cells, such as polymorphonuclear leukocytes, T-lymphocytes, histiocytes, macrophages and multinucleated giant cells in the thrombi and in all layers of the vessel wall, which are associated with endothelial cell proliferation and angiogenesis, collagen deposition and myofibroblast proliferation, were observed in histological samples of venous and arterial thrombi in patients affected by COVID 19. Endothelial damage can produce thrombosis in peripheral arteries and in the aorta, which may cause major vascular events, such as acute arterial ischemia (7).

It has yet to be elucidated whether inflammatory-associated changes (6) are a specific effect of coronavirus SARS-CoV-2

Figure 1. Gangrene of the right lower limb, demonstrating the effects of gangrene on the patient's calf. The patient is described as Case 2 above. The extent of dead tissue is evident.

Figure 2. Gangrene of the right lower limb of the patient described in Case 2. The extent of dead tissue is evident on her ankle and toes.

or a consequence of the 'cytokine storm' that precipitates the onset of the systemic inflammatory response syndrome, as observed in other viral diseases (8).

Hospitalized patients with an acute medical illness, including infections such as pneumonia, are at an increased risk of developing venous thromboembolism (VTE) (9,10). Prophylactic anticoagulation reduces the risk of developing VTE in acutely ill hospitalized patients (11-13), and the appropriate use of prophylaxis for VTE is covered by clinical practice guidelines (10,14,15). VTE risk stratification for hospitalized patients with COVID-19 should be performed (16). Hospitalized patients with COVID-19 who have respiratory failure or co-morbidities (e.g., active cancer or heart failure) (17), patients who are bedridden and those requiring intensive care, need to receive pharmacological VTE prophylaxis, unless contraindicated. The World Health Organization interim guidance statement recommends pharmacological prophylaxis [LMWH (preferred if available) or heparin 5,000 U subcutaneously twice daily] in adolescents and adults without contraindications (18), and mechanical prophylaxis (intermittent pneumatic compression devices) for those with contraindications (18,19).

While there are no data available specific to COVID-19, it is reasonable to employ individualized risk stratification for thrombotic and bleeding risks, followed by the consideration of extended prophylaxis (up to 45 days) for patients who are at a high risk of developing VTE (e.g., with reduced mobility, co-morbidities, such as active cancer and elevated D-dimer levels) who have a low risk of bleeding (20-22). The role of thromboprophylaxis in quarantined patients with mild COVID-19, although with significant co-morbidities, or for patients without COVID-19 who are less active due to quarantine, is uncertain. Such patients should be advised to stay active while at home.

While the awareness of venous antithrombotic prophylaxis in patients hospitalized with COVID-19 has increased, little attention has been paid to PAD. Patients with COVID-19 require close monitoring with regard to their cardiovascular risk (CVR) profile, which may increase due to the inflammatory state.

The second case presented herein is a typical example of the issue of delayed diagnosis of severe cardiovascular diseases during lockdown for COVID-19. Lockdown measures and recommendations may delay the clinical evaluation of patients with a fear of contracting the infection in a hospital or medical practice. Patients with limb ischemia are fragile and their outcome is negatively affected by the delay of the usual standard of care (3). As described in the second case of the present study, the patient did not have COVID-19; however, the isolation from her family and her fear of visiting the hospital eventually led to a fatal outcome. In addition, it may be argued that restrictive dispositions during lockdown have increased a certain depressive state in individuals living alone, due to the sudden physical isolation, which may result in a general lack of attention to their overall wellbeing. If treated properly and in a timely manner, it is believed that, despite the severity of the patient's clinical condition, the outcome would have been more favorable. This case highlights that healthcare organizations must also consider monitoring elderly patients, particularly those with known CVR factors. Telemedicine could also be implemented, particularly in emergency situations and cases of social isolation.

The third case presented herein demonstrates that the measures implemented during the lockdown period to reduce the spread of COVID-19 may have significant effects on known non-COVID-19 vascular patients, for whom regular follow-up with a physical examination and US is crucial for detect a possible worsening of their clinical condition. These patients may be 'lost to follow-up'.

The European Independent Foundation in Angiology/Vascular Medicine (VAS) recommendations for general measures in patients with VD or CVR factors during the SARS-CoV-2 epidemic underline the importance of follow-up for patients with VD or CVR upon SARS-CoV-2 infection. For patients with chronic disease, such as those with VD-CVR, regular medical follow-up is crucial for the improvement and preservation of good health. During the ongoing pandemic, patients with COVID-19 affected by VD-CVR and non-severe COVID-19 who received medical care at home, may be at a high risk of developing more severe disease and even death. Therefore, these patients require close follow-up and need to

be prioritized for hospital admission in the case of worsening of COVID-19 symptoms and/or worsening of their chronic pathology, such as cardiovascular and atherosclerotic disease.

The treatment of cardiovascular complications perhaps should be based on optimal and judicious implementation of guideline-based therapies; in addition, the use of antiplatelet agents, β-blockers, angiotensin-converting enzyme inhibitors and statins can curb systemic inflammation, stabilize the plaques and, possibly, prevent plaque destabilization that can lead to cardiovascular complications (5). It would also be useful to identify risk factors that may promote cardiovascular complications in patients with COVID-19 (5).

The registry of patients with COVID-19 with vascular diseases and vascular complications may be an important tool for identifying the pattern of cardiovascular complications and may aid in the development of a risk model for the stratification of these patients and the recommendation of personalized treatments.

Educational programs need to be elaborated for patients with PAD in order to increase their awareness on the importance of the adherence to the antihypertensive, antiplatelet, lipid-lowering and anti-hyperglycemic therapy, according to the recommendations of the relevant consensus statements and scientific societies. Physical activity (i.e., 6,000 steps per day), particularly during the periods of lockdown, is as crucial as medical therapy for patients with PAD, while respecting social distancing and applying self-protection measures.

Educational programs may also prove to useful for general practitioners (GPs), as it may help them recognize early signs of more severe PAD, particularly for patients who have discontinued their specialist follow-up, and may improve the communication between the GP and the angiology/vascular medicine specialist (23).

The VAS recommendations for the diagnosis of PAD during the SARS-CoV-2 outbreak emphasize that physicians need to be advised and be aware of the most common signs and symptoms of PAD (as it is an underdiagnosed vascular pathology) and to routinely perform appropriate physical examinations during home visits or regular consultations, including the measurement of ABI, particularly among the elderly, smokers and diabetic patients.

Patients with PAD are at a high risk of death and major leg amputation. A higher number of major amputations has been reported among patients with PAD (1). A higher number of amputations were performed at surgery departments, as described by Sena and Gallelli (24) in Italy.

In a number of hospitals, elective surgeries were postponed and only urgent surgical care was provided. Chiesa *et al* (25) reported the effects of the reorganization of vascular surgery in a large metropolitan hospital in Milan: Numerous outpatient activities were suspended, and only emergent and urgent vascular surgery was performed. As a consequence, more advanced grades of vascular diseases, such as gangrene, requiring more aggressive therapeutic treatments, and an increased number of cases of acute limb ischemia in patients with COVID-19 were observed during the later phase of the escalation of COVID-19 cases. A similar experience was reported by other vascular units: Elective surgeries were limited, with an overall negative impact on the outcomes of PAD and a higher rate of major limb amputations for critical limb ischemia (5).

The third case presented herein highlights that it is crucial to maintain follow-up, particularly of patients suffering from known PAD. Regular phone contact is necessary when it is not possible to assess the patient in an outpatient setting.

The 'lost syndrome' is a term referring to PAD. This is already an unrecognized disease under normal conditions and even more so during the pandemic, with diagnosis delayed or missed and patients lost to follow-up. Physicians must intensify their efforts to effectively treat these patients.

In conclusion, the experience of recent months should foster awareness regarding the potential negative impact of lockdown restrictions and reorganization of the healthcare system on vulnerable patient groups, such as those affected by PAD or other cardiovascular diseases. During the COVID-19 pandemic non-urgent vascular examinations were postponed and the focus was shifted to pandemic management. However, when urgent vascular examinations, such as those related to critical or acute limb ischemia, are required, a specialist assessment, including DUS, should not be postponed. Finally, prophylaxis against arterial and venous thrombotic events is crucial for patients with COVID-19, particularly those with a marked inflammatory state.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CP designed the study, and drafted and wrote the manuscript. BZ and LF were involved in the study design and edited the manuscript. SI and AV supervised the study and were also involved in the conception and design of the study. CP collected patient data. BZ and LF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the three patients whose cases are presented herein.

Patient consent for publication

Written informed consent was obtained from the three patients in the present study for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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