A case of COVID-19 with superficial thrombophlebitis caused by an indwelling peripheral venous catheter

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Research Article

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Abstract

Background:

COVID-19 is caused by SARS-CoV-2 infection, and cytokine storm and microthrombus formation affect the severity of the disease, which is often complicated by venous thrombosis due to a systemic hypercoagulable state. On the other hand, indwelling peripheral venous catheters can cause catheter-related bloodstream infections and venous thrombus formation, albeit less frequently.

Case presentation:

A 53-year-old man was admitted to the hospital with severe COVID-19. He had bilateral pneumonia and required ventilator management but recovered after steroid and anticoagulation. On the 26th day after onset, redness, swelling, and pain developed around the insertion site of the catheter placed in the cephalic vein of the left forearm. Vascular ultrasonography revealed a thrombus in this vein accompanied by inflammation in the surrounding tissues. Catheter-related bloodstream infection was suspected and vancomycin was administered; however, blood cultures were negative, leading to the diagnosis of non-infectious superficial thrombophlebitis. The skin findings improved after removal of the peripheral venous catheter.

Conclusions:

This case suggested that catheter placement in peripheral veins during COVID-19 treatment increases the risk of thrombus formation. Although anticoagulant therapy is able to control the systemic hypercoagulable state caused by COVID-19, indwelling catheters can induce a local hypercoagulable state, leading to superficial thrombophlebitis.

Introduction

Coronavirus disease 2019 (COVID-19) mainly affects the respiratory system, but there are many reports of complications of venous thromboembolism (VTE) such as pulmonary thromboembolism (PE) and deep vein thrombosis (DVT). There are few reports of thrombus formation in peripheral veins resulting in superficial thrombophlebitis. We report a rare case of COVID-19 with superficial thrombophlebitis due to a thrombus formed by an indwelling peripheral venous catheter.

Case Presentation

On the day following a dinner party with four friends, cough, anorexia, and general malaise developed, which exacerbated thereafter, and fever of 39°C was also observed. On the 16th day of onset, the patient visited his local physician who found infiltrative shadows in both lung fields on chest X-ray (Figure 1). On the same day, he was referred to a general hospital, where severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected by nasopharyngeal swab, and he was admitted with respiratory failure.
Chest computed tomography demonstrated ground-glass opacities and infiltrative shadows in the lower lobes of the bilateral lungs with a subpleural predominance (Figure 2), and he was diagnosed with severe COVID-19. Although high-flow nasal cannula (HFNC) was started, due to a deteriorating respiratory condition, he was intubated in the evening of the same day, and administered 6.6 mg of dexamethasone intravenously and enoxaparin sodium subcutaneously. However, on the 3rd day of hospitalization (18th day of onset), his respiratory condition did not improve. As extracorporeal membrane oxygenation (ECMO) was considered, he was transferred to our hospital on the same day. After admission to the intensive care unit (ICU), his treatment was continued and supine management was started (without remdesivir or tocilizumab). As the oxygen demand improved, he was extubated on the 6th day of transfer and HFNC was reintroduced, which was completed on the 10th day of transfer, and oxygen administration was completed on the 13th day of transfer. Dexamethasone was administered for 10 days, enoxaparin sodium was administered for 11 days, and the anticoagulant was changed to edoxaban.

On the 9th day of transfer to our hospital (26th day of onset), the peripheral venous catheter placed in the cephalic vein of the left forearm was removed. The next day, redness, swelling, and pain were observed around the site of catheter insertion (Figure 3). Blood tests revealed increased CRP (2.58 mg/dL on day 26 to 9.28 mg/dL on day 29). Although he did not have fever, catheter-related bloodstream infection (CRBSI) was suspected based on skin findings. Vancomycin (VCM) was started, but blood cultures were negative one week later and CRBSI was also negative, leading to the discontinuation of VCM. Vascular ultrasonography demonstrated a thrombus in the cephalic vein of the left forearm (Figure 4A, 4B), accompanied by inflammation in the surrounding tissues, which was diagnosed as superficial thrombophlebitis. D-dimer levels peaked on the 27th day of onset and decreased, and CRP and skin findings improved (Figure 3B). No evidence of DVT in the lower limbs was found on ultrasonography, but PE was not evaluated because contrast-enhanced CT was not performed. Although we did not consider infectious disease, cellulitis was unable to be excluded; therefore, cefditoren pivoxil was started the day after VCM was completed. After confirming improvement in the skin findings on the left forearm, both edoxaban and cefditoren pivoxil were discontinued after 2 weeks. The patient was discharged on the 23rd day of transfer (40th day of onset) with good progress.

**Discussion**

To the best of our knowledge, this is the first case report of COVID-19 with superficial thrombophlebitis induced by an indwelling peripheral venous catheter. There are few reports of superficial thrombophlebitis associated with COVID-19. Demirbas et al. \(^1\) reported only one case, but it was not in a peripheral vein with an indwelling catheter. There is a report on VTE from northern Italy \(^2\) in which superficial thrombophlebitis was observed in 7 of 101 COVID-19 patients who underwent ultrasonography, and only one case was in the cephalic vein as in the present case. However, there was no mention of whether it was an indwelling catheter, making the present case valuable.
In February 2020, SARS-CoV-2 infection was named COVID-19 by the WHO and it has since become a worldwide pandemic\textsuperscript{3}. COVID-19 mainly affects the respiratory system, causing a variety of symptoms ranging from mild flu-like symptoms to severe pneumonia, but effects on organs besides the respiratory system have also been reported\textsuperscript{4}. Venous thrombosis, such as PE and DVT, has been reported frequently, especially in patients requiring ICU management\textsuperscript{5-7}. Cytokine storm induced by SARS-CoV-2 infection is known to cause widespread microvascular and macrovascular thrombosis and organ failure\textsuperscript{8}. A report of lungs autopsied after COVID-19\textsuperscript{9} revealed severe vascular endothelial cell damage, resulting in the occlusion of alveolar capillaries by microthrombus formation. The angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-CoV-2, is highly expressed in the lungs, which is thought to be a target organ, but there is a report that ACE2 is also expressed in the vascular system, including endothelial cells and vascular smooth muscle cells\textsuperscript{10}. In this case, although the patient was receiving anticoagulant therapy, the excessive inflammation caused by SARS-CoV-2 damaging vascular endothelial cells in peripheral veins via ACE2 increased blood coagulation capacity, resulting in the risk of thrombus formation and thrombophlebitis.

Superficial thrombophlebitis is a disease in which a blood clot forms and obstructs a peripheral vein, causing inflammation of the vein, surrounding tissue, and skin. Most cases of thrombophlebitis develop in the veins of the lower limbs\textsuperscript{11}, but it can also develop in the upper limbs due to endogenous factors, such as Buerger's disease\textsuperscript{12}, which damages the blood vessels themselves, or due to exogenous factors such as trauma or catheterization\textsuperscript{13}. The thrombophlebitis in this case had no relationship with endogenous disease or trauma. Although a systemic search for thrombus was not performed, DVT was not observed, and as it was considered to be local hypercoagulability rather than systemic in that there were no notable findings suggestive of thrombosis in other organs, the catheter placed in the peripheral vein may have damaged the vascular endothelial cells, causing blood stagnation and possibly increasing the coagulation abnormalities of COVID-19, leading to thrombus formation and superficial thrombophlebitis.

Other factors can also lead to thrombus formation and phlebitis. Thrombosis due to central venous catheters is associated with CRBSI\textsuperscript{14}. In addition, Hernandez et al.\textsuperscript{15} reported that the rate of thrombus formation was three-times higher in the group with CRBSI than in the group without CRBSI in a study of hemodialysis catheters. This case was initially thought to be CRBSI because of the skin findings, increased inflammatory reaction on blood testing, and intravenous thrombus, but as CRBSI is rarely observed with peripheral venous catheters (0.2 cases per 100 catheters\textsuperscript{16}) and the blood culture was initially negative (catheter tip culture test was not performed), CRBSI was excluded. Peripheral venous catheters are left in place with a heparin lock, but it has been reported that heparin promotes the adhesion of coagulase negative Staphylococcus (CNS) to the catheter\textsuperscript{17} and that regular heparin use, even at doses as low as 250-500 units per day, can cause thromboembolism\textsuperscript{18}. However, in this case, continuous intravenous infusion of Ringer's acetate solution, furosemide, and dexmedetomidine was performed, and heparin was not administered, excluding thrombus formation due to heparin. The CDC recommends
changing peripheral venous catheters every 72 to 96 hours, but also notes that catheters can be left in place longer if the venous access site is limited and there is no evidence of phlebitis or infection\(^{19}\). In this case, the catheter was placed for less than 3 days (the date of catheter placement was unknown, but our ICU has a rule of regular replacement every 3 days), and the skin findings were unremarkable from the time of catheter insertion to the time of removal. Anticoagulant therapy against COVID-19 may act as a prophylactic against thrombus formation from the indwelling catheter. Therefore, preventing the superficial thrombophlebitis in this case may have been difficult despite regular skin observation, adherence to proper catheterization duration, and prophylactic anticoagulation.

We reported a valuable case of COVID-19 complicated by thrombophlebitis in the cephalic vein of the left forearm. In this case, superficial thrombophlebitis developed even while the patient was receiving anticoagulant therapy for COVID-19, suggesting that catheter placement in peripheral veins during COVID-19 treatment is a risk factor for thrombus formation. Although securing the peripheral venous route for COVID-19 is a frequently performed procedure, there have been few reports of superficial thrombophlebitis and the reason for its development in the present case is unknown. The longer the catheter remains in place, the greater the risk of thrombus formation and bloodstream infection\(^{20}\); therefore, prompt removal should be considered when no longer needed.

**Declarations**

Ethics approval and consent to participate:

The approval of research ethics committee was not required for the publication of this case report.

Consent for publication:

Informed consent was received from the patient.

Availability of data and material:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests:

The authors declare that they have no competing interests.
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Authors’ contributions:

HT treated the patient and wrote the manuscript. All authors read and approved the final manuscript.

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Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; VTE: Venous thromboembolism; PE: Pulmonary thromboembolism; DVT: Deep vein thrombosis; HFNC: High-flow nasal cannula; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; CRBSI: Catheter-related bloodstream infections; VCM: Vancomycin; ACE2: Angiotensin-converting enzyme 2

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**Figures**
Figure 1

Chest X-ray on admission to the referring hospital. Ground-glass opacities (GGO) and infiltrative shadows were observed in both lung fields.
Figure 2

Chest computed tomography on admission to the referring hospital. GGO and infiltrative shadows were observed in the lower lobes of the bilateral lungs with a subpleural predominance.

Figure 3

Image of the left forearm. (A) Redness and swelling were observed around the insertion site of the catheter in the cephalic vein on the 26th day of onset. (B) After removal of the catheter, the redness and swelling improved.
Figure 4

Vascular ultrasonography showed a thrombus in the lumen of the cephalic vein of the left forearm (red arrow), accompanied by inflammatory findings in adjacent tissues (yellow arrow). (A) Longitudinal view. (B) Transverse view.