

COVID-19 and Phlegmasia cerulea dolens: a case report and review of the literature

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SUMMARY

COVID-19 affects respiratory system and may also lead to severe deep vein thrombosis (DVT), known as phlegmasia cerulea dolens (PCD). We report the case of a 35-year-old woman who presented with a two-day history of pain and swelling in her left lower extremity. She had a history of COVID-19 infection three weeks prior to presentation. Ultrasound doppler showed acute left DVT extending from the left external iliac to the popliteal vein. PCD was diagnosed based on her physical examinations and doppler ultrasound reports. We also searched published case reports related to PCD and tabulated 13 cases for discussion. Most of the patients were more than 50 years old and had increased hypercoagulable states. Half of the patients had acute pulmonary embolism, and the case fatality rate was approximately 25%. The anticoagulant was the initial treatment of choice, but most patients needed surgical intervention.

INTRODUCTION

Phlegmasia cerulea dolens (PCD) is a rare and severe form of deep vein thrombosis (DVT).¹ PCD often manifests as a triad of pain in the affected limb, oedema and cyanosis.^{1,2} Diagnosis is made based on physical examination findings and doppler ultrasonography.³ Life-threatening sequelae of PCD include acute pulmonary embolism (PE), limb amputation, and death.³

The first case of SARS-CoV-2 was reported in December 2019,⁴ and the World Health Organisation (WHO) declared the disease, later known as COVID-19, a global pandemic in March 2020.⁴ It is known to be associated with thromboembolic events.^{1,2,5-7} We describe a rare thromboembolic event that led to PCD in a COVID-19 patient. A review of the literature involving similar cases that have occurred worldwide is also highlighted, including the interventions.

CASE PRESENTATION

A 35-year-old woman with type 2 diabetes mellitus (DM) and hypertension presented to the Emergency Department (ED), Hospital Universiti Sains Malaysia with a two-day history of pain and swelling of the left lower extremity (LLE).

Based on further history, she has been taking a combined oral contraceptive pill (COCP) for the past year after her last

pregnancy. She also had undergone an emergency lower segment caesarean section for breech presentation. Three weeks prior to this presentation, she was treated for a category 2 COVID-19 infection and was discharged well.

On arrival at the ED, she was alert and conscious. Her vital signs were blood pressure of 152/98 mmHg, heart rate of 121 beats per minute, afebrile (36.4°C) and oxygen saturation of 98% in room air. On examination, her entire LLE was swollen, tender to palpation, appeared cyanotic and shiny with pitting oedema up to the mid-shin. Her distal pulses and sensation were intact. There was also a discrepancy in her calves' circumferences. Her right calf was measured at 40 cm, while her left calf was measured at 45 cm (Figure 1).

A formal doppler ultrasound of the LLE was performed, and the radiology team found dilated deep veins of the left lower limb with non-compressible distal left external iliac, left common femoral, proximal and midpart of left superficial femoral and left popliteal veins, with the presence of echogenic thrombus and no colour doppler flow seen within (Figure 2 and 3). It was reported as an acute left DVT extending from the left external iliac to the left popliteal veins.

Based on the clinical examination findings and LLE ultrasound doppler report, she was diagnosed with LLE PCD, aligned with the same diagnosis from the medical team. She was started on intravenous heparin with a loading dose of 80 IU per kg, followed by infusion of 18 IU per kg per hour in the ED. The medical team opted for subcutaneous injection of fondaparinux 7.5 mg once a day (OD) and changed to oral rivaroxaban once available with a dose of 15 mg BD for 3 weeks, followed by 20 mg OD for 6 months.

She was well during the hospital stay and was counselled for intrauterine contraceptive devices by the Obstetrics & Gynaecology (O&G) team for her future contraceptive option. She was discharged well and was given a clinic and an LLE doppler ultrasound appointment 6 months after discharge for reassessment.

DISCUSSION

This is the first COVID-19 patient with PCD reported in an Asian country, and it involves Malay ethnicity. The patient was on oral contraceptive pill (OCP), which is a known risk factor for thromboembolic events. Complicated by the

This article was accepted: 30 November 2023

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Table 1: Summary of Case Reports

Study / Case Report	Setting during the diagnosis	Ethnic (Country)	Gender	Age (years)	Extremity involved	Comorbidities	COVID-19 category	Onset to PCD	Other risk factor/s for thromboembolism	Lung findings	Associated with pulmonary embolism	Inter-vention	Out-come
Akkari 2020 ⁸	NA	African American (USA)	Male	61	Left lower extremity	Nil	5	Asymptomatic	Nil	CT chest bilateral patchy ground-glass opacities	Yes, CT chest left main pulmonary artery PE	Emergent fasciotomy	Expired
Bamgboje 2020 ⁴	Ward	Caucasian (USA)	Male	61	Both lower extremities	HPT	4	7 days	APLS	Chest X-ray on admission showed bibasilar pulmonary infiltrates compatible with pneumonia	No	Heparin	Discharged
Chun 2020 ¹⁰	Vascular Surgery	Caucasian (USA)	Male	51	Left lower extremity	Congenital tricuspid atresia, pulmonic stenosis, recurrent paroxysmal AF on long term warfarin	5	2 days	APLS	NA	No	Surgical - lower extremity venography, placement of a retrievable filter, and mechanical thrombectomy	Left BKA on hospital day 39 and discharged 9 days later, with warfarin therapy
Hembd 2021 ⁵	Plastic Surgery	Caucasian (USA)	Female	54	Right upper extremity	DM, refractory ph-like lymphoblastic leukemia with indwelling PICC line, chemotherapy related pancytopenia	2	9 days	Leukemia	NA	NA	Heparin and bedside fasciotomy	Expired
Jan 2021 ⁹	Outpatient department	Caucasian (USA)	Male	42	Left lower extremity	NA	2	2 weeks	History of DVT	CTA pulmonary infarcts bilaterally, multiple mixed cavitating and non-cavitating lesions in both lungs associated with ground glass haze and small left pleural effusion, multiple large mediastinal and upper abdominal lymph nodes, hilar lymph nodes eroding walls of bilateral pulmonary arteries.	Yes, CTA	Surgical thrombectomy	Anticoagulant and discharged

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Morales 2020 ⁶	ED	Caucasian (USA)	Male	55	Right lower extremity	MVA with multiple surgeries complicated with DVT and IVC filter placed, hypertension	2	3 weeks	APLS	Chest x-ray revealed bilateral patchy infiltrates	Yes, CT chest subsegmental PE in the medial right middle lobe	Medical - IV alteplase 50mg and heparin	Admitted to ICU, continued on heparin, transitioned to oral anticoagulant, discharged on day 7
Visweswaran 2021 ²	Paediatric department	Caucasian (USA)	Female	12	Left lower extremity	Nil	1	5 days	APLS	Pulmonary angiography confirmed extensive emboli in the superior, middle, and inferior segments of the right lung; the lingular segment of the left lung; and interlobular pulmonary arteries	Yes, Echocardiogram revealed severe right ventricular dilation with severe hypokinesis	Heparin and percutaneous mechanical venous thrombectomy	Discharged with enoxaparin
Moraes 2021 ¹	ED	Caucasian (USA)	Male	47	Left lower extremity	DM HPT	2	7 days	Nil	V/Q scan revealed multiple, large, segmental perfusion defects in the bilaterallungs	Yes, Bedside echocardiogram revealed evidence of acute right heart strain with a dilated right ventricle and paradoxical septal wall motion	Catheter directed alteplase by IR, IVC filter placement	Discharged with rivaroxaban
Orso 2021 ⁷	ICU	Caucasian (Italy)	Male	64	Both lower extremities	Obese, HPT, AF, type 2 DM, CKD, OSA, chronic venous insufficiency	5	NA	Nil	Lung and cardiac ultrasound were compatible with severe interstitial pneumonia and with no signs of pressure overload of the right heart	NA	Heparin and iloprost, CVWH	Expired
Abdulmutaali 2021 ¹¹	Internal Medicine	Arab (Saudi Arabia)	Female	62	Left lower extremity	DM, HPT	2	5 days	Nil	NA	Yes, computed tomography of the patient's chest showed bilateral PE	Heparin, fasciotomy and AKA	Discharged with anticoagulant

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Avdeev 2021 ³	ED	Caucasian (Russia)	Female	61	Right upper extremity	Type 2 DM HPT	2	3 days	Nil	NA	NA	Heparin and emergency percutaneous mechanical thrombectomy	Discharged with apixaban
Alghamdi 2022 ¹⁹	ED	Arab (Saudi Arabia)	Male	58	Left lower extremity	Nil	3	3 days	May-Thurner syndrome	Bilateral peripheral patchy opacities	No	Heparin, IVC filter, catheter-directed alteplase, aspiration	Discharged with anticoagulant
Cohen 2023 ¹²	NA	Caucasian (USA)	Male	44	Bilateral lower extremities	DM	NA	NA	DVT, PE with IVC filter, PAD	NA	Past history of PE	Heparin, catheter-directed alteplase, followed by thrombectomy and suction	NA
Current case	ED	Malay (Malaysia)	Female	35	Left lower extremity	DM, HPT HPL	2	4 weeks	COCP	NA	No	Fondaparinux and rivaroxaban	Discharged with anticoagulant

COVID-19 category (CAT): CAT 1=asymptomatic; CAT 2=symptomatic, no pneumonia; CAT 3=symptomatic, pneumonia; CAT 4=symptomatic, pneumonia, requiring supplemental oxygen; CAT 5=critically ill with multi-organ involvement.

Abbreviation: AF=atrial fibrillation; AKA=above knee amputation; APLS=antiphospholipid syndrome; BKA=below knee amputation; CKD=chronic kidney disease; COCP=combined oral contraceptive pill; CT=computed tomography; CTA=CT angiography; CVWH=continuous veno-venous hemofiltration; DM=diabetes mellitus; DVT=deep venous thrombosis; ED=emergency department; HPL=hyperlipidemia; HPT=hypertension; ICU=intensive care unit; IV=intravenous; IVC=inferior vena cava; MVA=motor vehicle accident; NA=not available; OSA=obstructive sleep apnea; PCD=phlegmasia cerulea dolens; PE=pulmonary embolism; PICC=peripheral inserted central catheter; PAD=peripheral arterial disease; USA=United States of America.

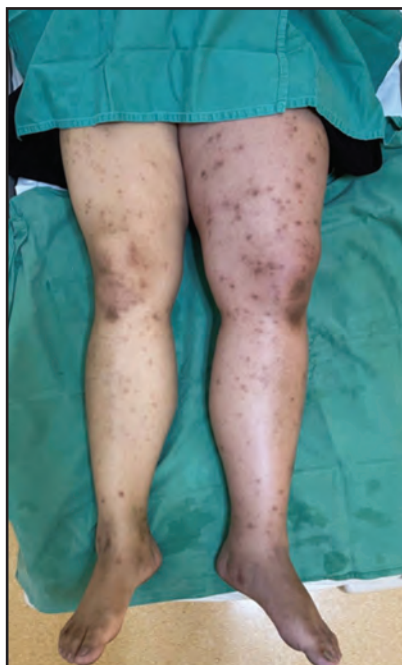


Fig. 1: Swollen, shiny and bluish discoloration of left lower extremity extending from thigh until the foot.

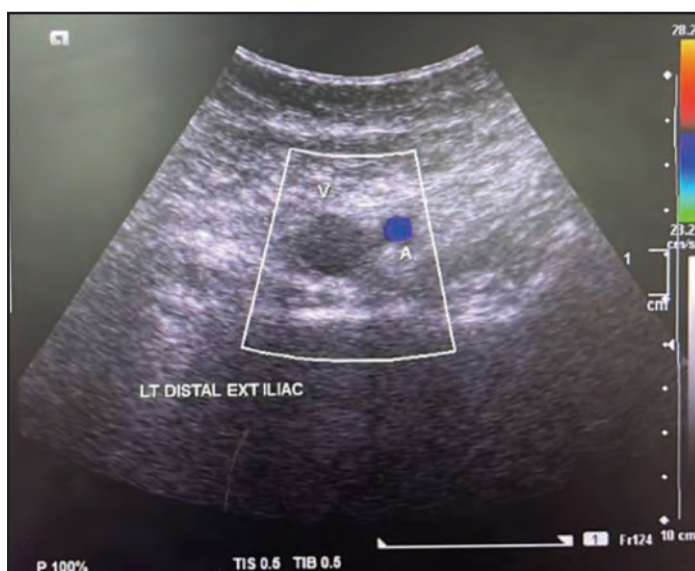


Fig. 2: Colour doppler flow not seen within visualised left distal external iliac vein with presence of echogenic thrombus within.

COVID-19 infection, she developed PCD a month later. Based on the published case reports, there were variations in the onset of PCD among post-COVID-19 patients, as summarised in Table I. Most of the cases were reported in the USA.^{1,2,4-6,8-10} The outcome of patients also varied, in which three patients passed away due to PCD and its complications.^{5,7,8}

There was no specific gender preference, and most of the cases involved patients who were more than 50 years of age. There was only one paediatric patient who had PCD involving the LLE.² LLE is more commonly affected, possibly due to the compression of the left common iliac vein by the right common iliac artery. Based on the series of previous case reports (refer Table I), it appears that there is no specific

COVID-19 category that is associated with developing PCD. Diabetes and hypertension are common comorbidities. The onset of COVID-19 until the diagnosis of PCD varies from as early as two days to as long as 1 month, as reported in the current case. However, PCD can also manifest in an asymptomatic COVID-19 patient,⁸ and some of whom exhibit no risk factors for thromboembolism.^{1,3,7,8,11} Among the COVID-19 patients, the most common risk factors for thromboembolism is antiphospholipid syndrome (APLS),^{2,4,6,10} followed by a history of DVT,^{9,12} leukaemia,⁵ May-Thurner syndrome¹³ and COCP. In addition to this, many COVID-19 patients show elevated D-dimer levels and hypercoagulable states, contributing to an increased incidence of thromboembolic events.¹² Viral illnesses such as SARS-CoV-2

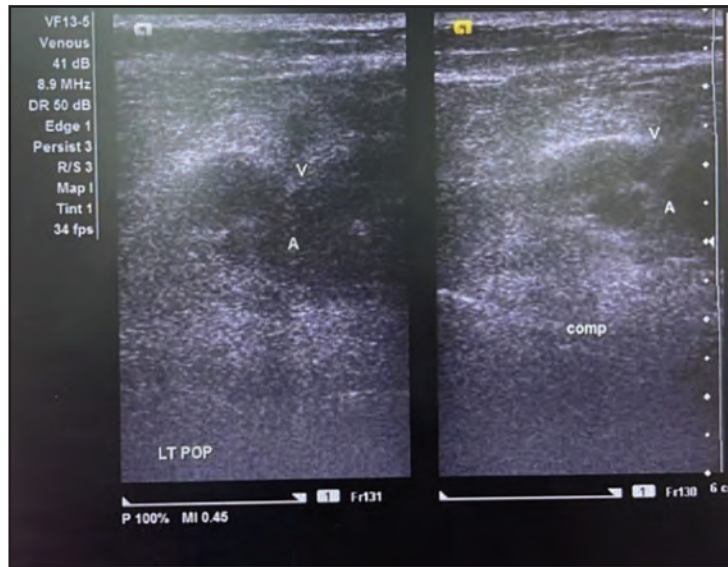


Fig. 3: Non compressible left popliteal vein with presence of echogenic thrombus within.

also have been linked to transiently elevated antiphospholipid antibodies, further augmenting the hypercoagulable state.¹³

Lung findings reported in the cases were ground-glass opacities,^{8,9} bilateral pulmonary infiltrates,^{4,6} and severe interstitial disease.⁷ Six cases eventually led to acute pulmonary embolism (PE), four of which reported the involvement of bilateral lungs.^{1,2,9,11} Most cases were administered heparin before proceeding to other modes of treatment. Four cases reported the use of alteplase in treating PCD.^{1,6,12,13} Surgical interventions in PCD were emergency mechanical thrombectomy in five cases,^{2,3,9,10,13} emergency fasciotomy in three cases,^{5,8,11} and filter insertion in two cases.^{1,10} In this case, our patient responded well to the treatment and was discharged alive. She did not develop any PE, and no surgical intervention was required.

CONCLUSION

COVID-19 patients have higher hypercoagulable states and may lead to phlegmasia cerulea dolens (PCD) and its complications. Half of the patients had acute pulmonary embolism (PE), and anticoagulants were the initial treatment of choice during presentation. Surgical interventions such as fasciotomy and thrombectomy may be required if the condition worsens.

REFERENCES

- Moraes B, Hashemi A, Mancheno K, ObanDo M, Marra E, Obano M, et al. Hypercoagulability due to COVID-19 leading to impending phlegmasia cerulea dolens and sub-massive bilateral pulmonary embolism. *J Cureus* 2021; 13(8): 1-5
- Visveswaran GK, Morparia K, Narang S, Sturt C, Divita M, Voigt B, 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: 281-84.e1.
- Avdeev SN, Nekludova GV, Tsareva NA, Yaroshetskiy AI, Merzhoeva ZM, Nuralieva GS, et al. Pain, swelling and blue discoloration of right hand in a COVID-19 patient. *Ann Emerg Med* 2021; 77(6): 657.
- Bamgboje A, Hong J, Mushiyeve 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: e928342-1.
- Hembd A, Kim H, Lahsaei P, Haddock NT, Teotia SS. Upper-extremity phlegmasia cerulea dolens with compartment syndrome in coronavirus disease 2019 sepsis. *J Hand Surg* 2022; 47(7): 693.e1-e3.
- Morales MH, Leigh CL, Simon EL. COVID-19 infection with extensive thrombosis: a case of phlegmasia cerulea dolens. *Am J Emerg Med* 2020; 38(9): 1978.e1.
- Orso D, Mattuzzi L, Scapol S, Delrio S, Vetrugno L, Bove T. Phlegmasia cerulea dolens superimposed on disseminated intravascular coagulation in COVID-19. *J Acta Bio Medica: Atenei Parmensis* 2021; 92(4): 1-4
- Akkari R, Schwartz B. Phlegmasia cerulea dolens: an atypical COVID-19 presentation. *Chest* 2020; 158(4): A2090.
- Jan A, Khizar HM. Phlegmasia cerulea dolens (PCD) as a complication of COVID-19: case report. *CTSNet, Inc. Media*; 2021.
- 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(4): 653-56.
- Abdulmutaali W, Alamri M. Extensive thrombosis (DVT/PE) with phlegmasia cerulea dolens/amputation and compartment syndrome with COVID-19: a case report. *IJMDC* 2021; 5(4): 1100-102.
- Cohen S, Lynch J. COVID-19-Induced phlegmasia cerulea dolens. *Cureus* 2023; 15(1): e33644. doi: 10.7759/cureus.33644.
- Alghamdi L, Alattab N, Alwohaibi A, Alotaibi YH, AlSheef M. Phlegmasia cerulea dolens secondary to COVID-19 and May-Thurner syndrome: a case report. *Cureus* 2022; 14(1): e21301.