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Phlegmasia cerulea dolens complicated by methylenetetrahydrofolate reductase genetic mutation

Jason A. Fried, Lauren M. Wright

ABSTRACT

Introduction: Deep venous thrombosis (DVT) is the formation of a blood clot within a deep vein. Phlegmasia cerulea dolens (PCD) represents a critical acute consequence of DVT. The PCD is a condition caused by massive iliofemoral thrombosis that produces severe venous congestion and obstruction of arterial flow; eventually, causing ischemia in the affected extremity. The treatment goals of PCD are to restore venous outflow by removing thrombus burden, prevent additional thrombus formation, and maintain collateral circulation. However, no therapeutic algorithms exist for PCD.

Case Report: We report PCD in a 55-year-old male with a significant past medical history for multiple venous thromboembolisms, requiring placement of an inferior vena cava filter and lifetime anticoagulation. Clinical presentation and accompanying venous duplex results led to the diagnosis of PCD. The 9th American College of Chest Physicians Consensus Conference on Antithrombotic and Thrombolytic Therapy created guidelines for treatment of acute DVT in the absence of gangrene. Guidelines advise to withhold thrombolysis and percutaneous or surgical procedure until treatment with therapeutic heparin anticoagulation proves to be inadequate. Conservative treatment with therapeutic anticoagulation was unsuccessful. therefore, catheter directed thrombolytic therapy, venoplasty, and stent placement were implemented.

Conclusion: Due to possible associated morbidity and mortality, it is recommended to implement therapy soon after diagnosis of PCD. It is hoped that this report will provide guidance in management and assist to develop an evidence-based treatment algorithm for PCD.

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Keywords: Deep venous thrombosis, Hypercoagulable, Phlegmasia cerulea dolens, Thrombolysis

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INTRODUCTION

Deep venous thrombosis (DVT) is the formation of a blood clot within a deep vein [1]. Principles of Virchow's triad—venous stasis, hypercoagulability, and endothelial injury—are postulated as the cause of venous

thrombosis. Non-specific physical examination findings of the extremity may include pain, swelling, erythema, prominent superficial veins, pain with passive dorsiflexion, and peripheral cyanosis [2]. Phlegmasia cerulea dolens (PCD) represents a critical acute consequence of DVT. PCD—"blue, painful leg" or "blue phlebitis" [3]—is a condition caused by massive iliofemoral thrombosis that produces severe venous congestion and obstruction of arterial flow; eventually, causing ischemia in the affected extremity [2, 3]. The PCD is an uncommon but fulminate manifestation of venous thrombosis, with high morbidity and mortality, and without a developed standard of care [3–5].

CASE REPORT

A 55-year-old male presented to the emergency department complaining of back pain of one day duration. Patient described the pain as severe, dull, with radiation to left buttock. Associated symptoms are paresthesias of bilateral lower extremities, left lower quadrant abdominal pain, and shortness of breath. Patient was a non-smoker with a past medical history significant for coronary artery disease, myocardial infarction status post four vessel coronary artery bypass graft, diabetes mellitus, congestive heart failure, cocaine abuse with cessation six months prior to admission, and multiple venous thromboembolisms requiring placement of an inferior vena cava filter and lifetime anticoagulation—rivaroxaban.

Physical examination revealed tenderness to palpation of left abdomen, bilateral flanks, and lumbar spine. Vascular examination included bilateral warm lower extremities, capillary refill less than two seconds, palpable femoral and posterior tibial (PT) pulses with dorsalis pedis (DP) Doppler signals, and no neurologic deficits. Vital signs and cell counts were within normal limits with a lactic acid of 3.1 mmol/L. Computed tomography (CT) scan of the abdomen and pelvis with intravenous and oral contrast revealed distal para-aortic and left retroperitoneal stranding, interpreted as a probable hematoma.

Patient was admitted to the medicine service with orders to hold anticoagulant therapy. On the second hospital day, patient complained of increasing bilateral leg pain—"tightness"—with subsequent change in vascular examination to bilateral bluish lower extremities which were edematous, tender to palpation, delayed capillary refill, no palpable lower extremity pulses, and bilateral PT Doppler signals. Sensation and motor function remained intact; however, he was unable to bear weight due to extreme pain. Vascular surgery was consulted. Computed tomography angiogram of the aorta with bilateral run-offs revealed diminished blood flow and atherosclerotic changes in the vessels below the knee, more apparent on the left than the right. Lower extremity venous duplex showed DVTs of bilateral lower extremities from the common femoral to distal posterior tibial, peroneal, and gastrocnemius veins.

The patient had not been on anticoagulant therapy due to concerns related to the retroperitoneal hematoma. However, considering the above duplex and clinical findings of PCD, the benefits outweighed the risks and therapeutic heparin [80 units/kg IV bolus, then continuous infusion of 18 units/kg/hr] with leg elevation was initiated. The following day, an interval CT of the abdomen and pelvis with intravenous contrast confirmed stability of the retroperitoneal hematoma. After five days of therapeutic heparin, the patient's clinical response was inadequate due to progressive pain and discoloration of bilateral lower extremities; therefore, decision was made to provide catheter directed thrombolytic therapy. He was taken to the vascular suite for venogram (Figure 1) and a Cragg–McNamera® (Micro Therapeutics Inc., Irvine, CA) catheter was placed for directed thrombolytic therapy (catheter Alteplase rate of 0.5 mg/hr and sheath heparin rate of 500 U/hr). Serial coagulation profiles were monitored and thrombolytic therapy was adjusted accordingly. Postoperative day-one, the patient returned to the vascular suite for interval venography, which revealed decrease in thrombus burden. Thrombolytic therapy was continued and patient returned to the vascular suite postoperative day-two. Venogram showed a patent right iliac vein and vena cava with IVC filter intact. The left external iliac vein had residual thrombus; therefore, venoplasty with 14/100 LifeStar® stent (Bard Peripheral Vascular, Tempe, Arizona) was deployed with subsequent expansion with a 14/40 Atlas® balloon (Bard Peripheral Vascular, Tempe, Arizona). Completion venography revealed a patent venous system with no extravasation or residual stenosis (Figure 2).

Postoperative course consisted of symptomatic treatment and serial vascular examinations. Etiology of condition remained unclear; therefore, hematology/oncology was consulted to exclude underlying malignancy and hypercoagulable state. Patient was found to be hypercoagulable due to a genetic mutation of methylenetetrahydrofolate reductase. The patient was discharged on postoperative day-six, with resolution of presenting symptoms and instructions for resumption of daily activities without functional limitations and continuation of vitamin-K-antagonist. Follow-up at 2nd month and 20th month revealed no recurrence of clinical symptoms.

DISCUSSION

Pathogenesis

Phlegmasia cerulea dolens (PCD) is a rare syndrome with pathogenesis of massive iliofemoral thrombosis causing total or near total venous occlusion. Subsequently, substantial increase in venous pressure produces parallel increase in tissue pressure with consequential fluid sequestration, edema, compromise of arterial circulation,

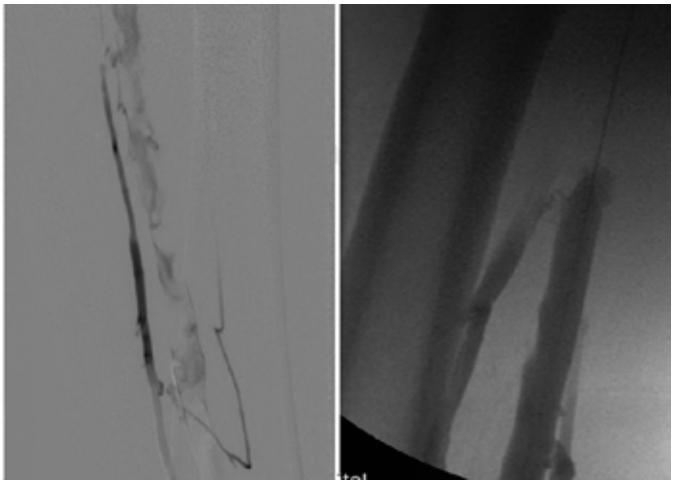

Figure 1: Venogram—extensive iliofemoral occlusive deep venous thrombosis. (A) Right femoral vein, and (B) Left femoral vein.

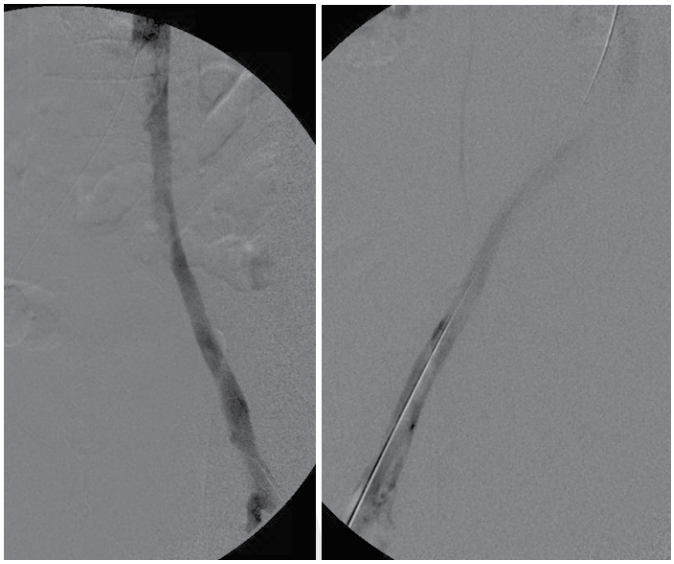

Figure 2: Venogram—completion venogram showing improved patency and flow after 48 hours catheter directed thrombolysis. (A) Right iliac vein and vena cava, and (B) Left iliac vein—venoplasty and stent placement.

and ischemia in the affected extremity [2–4]. Risk factors for development of DVT into PCD include malignancy, hypercoagulable states, previous DVT, trauma, inferior vena cava filter, contraceptive agents, and venous stasis [5]. Of these, malignancy is the most common etiology, with reported rates of 33% [4]. Prompt diagnosis and implementation of treatment is the basis to prevent complications such as gangrene [40–60%], amputation [20–50%], and death [25–40%]—pulmonary embolism being responsible for 30% of deaths [3–6].

Diagnosis

Phlegmasia cerulea dolens is classified based on severity—non-complicated, impending venous gangrene, or venous gangrene [4]. Diagnosis is established by physical examination and duplex ultrasonography (US) [3]. The PCD is clinically defined as a triad of acute extremity edema, cyanosis, and ischemic pain [5]. Ultrasonography is considered first-line imaging due to sensitivity and specificity in diagnosis of symptomatic proximal DVTs, 97% and 94% respectively; detection of occlusion in arteries and veins; and ability to characterize flow [7, 8]. Alternative diagnostic imaging being CT scan and magnetic resonance imaging scan, with catheter venography and arteriography being the gold standard due to ability to confirm diagnosis, help direct treatment from mapping of circulation, and be therapeutic [8].

Surgical strategy

The treatment goals of PCD are to restore venous outflow by removing thrombus burden, prevent additional thrombus formation, and maintain collateral circulation [4, 5]. No therapeutic algorithms exist for PCD. However, the 9th American College of Chest Physicians Consensus Conference on Antithrombotic and Thrombolytic Therapy created guidelines for the treatment of acute DVT in the absence of gangrene. Guidelines advise to withhold thrombolysis and percutaneous or surgical procedure until treatment with therapeutic heparin anticoagulation proves to be inadequate [9]. Conservative therapies for PCD involve elevation of the affected extremity, therapeutic heparin anticoagulation, and fluid resuscitation [3]. If clinical improvement inadequate or massive thrombosis with impending gangrene at presentation, thrombolysis is indicated. Thrombectomy—percutaneous or surgical—is implemented when there is contraindication to thrombolysis or in conjunction with thrombolysis; furthermore, percutaneous transluminal angioplasty with or without stenting and/or fasciotomy are supplementary treatment options depending resolution of thrombus burden and symptoms [3–6].

Defining optimal treatment with current knowledge is impracticable due to the paucity of data and quality studies [3, 10]. An international registry has been suggested to record all cases of PCD, which would assist with creation of an evidence-based approach to treatment [3]. Overall, further structured reporting of PCD is needed in order to augment understanding and education of the efficacy and safety of treatment strategies.

CONCLUSION

Phlegmasia cerulea dolens (PCD) is an uncommon but critical acute consequence of deep venous thrombosis (DVT). Due to the possible associated morbidity and mortality, prompt diagnosis and implementation of therapy are recommended. It is hoped that this report will provide guidance in management and assist to develop an evidence-based treatment algorithm for PCD.

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Author Contributions

Jason Fried – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising report critically for important intellectual content, Final approval of the version to be published
Lauren Wright – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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