Scientific Research Publishing

Case Reports in Clinical Medicine, 2023, 12, 312-323
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Analysis and Literature Review of Deep Vein Thrombosis Related Phlegmasia Cerulea Dolens Diagnosis in Critically Patients

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How to cite this paper: Zhang, Q., Yang, L. and Chang, L. (2023) Analysis and Literature Review of Deep Vein Thrombosis Related Phlegmasia Cerulea Dolens Diagnosis in Critically Patients. *Case Reports in Clinical Medicine*, **12**, 312-323.
https://doi.org/10.4236/crcm.2023.128044

Received: May 25, 2023
Accepted: August 20, 2023
Published: August 23, 2023

Abstract

Goal: The purpose of this research is to analyze the clinical characteristics, diagnosis, treatment, and prognosis of critical care patients with phlegmasia cerulea dolens (PCD) caused by deep vein thrombosis. Our goal is to improve both awareness and early diagnosis and treatment of rare clinical diseases. Furthermore, we aim to examine advancements in the diagnosis and treatment of deep vein thrombosis. **Method:** The clinical information of patients with PCD received in 2022 was subject to retrospective analysis. The author conducted a search of 191 publications with a focus on PCD, from January 2010 to July 2022, from databases such as the China National Knowledge Infrastructure (CNKI), Wanfang Data, PubMed, etc. The results were used to summarize the examinations, diagnostic criteria, and treatment progress of PCD patients. Additionally, the author conducted another search using keywords such as "Venous thromboembolism" and "Anticoagulant drugs" to summarize research progress in anticoagulant drugs and the treatment of VTE. The search was limited to relevant. **Outcome:** Six months prior to admission, the patient, a 68-year-old female, developed sunken edema and cyanosis in both her lower extremities and was diagnosed with lower extremity deep vein thrombosis complicated by PCD, lower extremity ischemic necrosis, and septicemia. This diagnosis was made using a combination of CT and lower extremity vascular ultrasound-related examinations, as well as a significantly elevated D-dimer value. Despite active treatment and aggressive measures, such as anti-infection, organ function maintenance, anticoagulation, and improvement of microcirculatory disorders, the patient's family declined corresponding surgical treatment and interventional surgery for the lower extremity due to objective factors, and the patient ultimately succumbed to her illness. The clinical characteristics of this patient were similar to those of

the 14 cases of PCD reported by Xie Fei *et al.* in 2022. **Conclusion:** For patients with malignancy, it is crucial to start anticoagulation and physical prevention of DVT early on. Patients with DVT complicated by PCD have a variety of surgical options available to them, including surgical embolization or PMT (percutaneous mechanical thrombus ablation), CDT (catheter contact thrombolysis), and fascial ventriculotomy decompression [1]. Additionally, it may be necessary to place an inferior venous filter. Although the incidence of this disease is low accounting for approximately 5% of all patients with iliofemoral deep vein thrombosis [2], the prognosis is poor, as the mortality rate can reach up to 40% - 60% due to venous gangrene, with an overall mortality rate of 20% - 40% [3]. To increase the survival rate, it is important to diagnose and treat this disease as early as possible.

Keywords

Malignant Tumor, Deep Vein Thrombosis, PCD

1. Background

Phlegmasia cerulea dolens (PCD) is a rare but life-threatening complication of deep venous thrombosis (DVT) of the lower extremities, which is the most severe form of acute DVT, whether caused by primary or secondary iliac vein thrombosis [4]. PCD is accompanied by the classic "triad" of pain, swelling, and cyanosis when the thrombus extensively invades the intramuscular venous plexus. The amputation rate is between 50% and 55% if the thrombus extends to the majority of the affected limb or the entire venous system, especially the deep femoral vein, so that the lower limb veins are in severe reflux obstruction, which is invariably accompanied by femoral artery spasm, that is, PCD. PCD accounts for approximately 5% of all iliofemoral vein thrombosis patients. It begins abruptly with pain, widespread swelling, tight and shiny skin, bruising, blistering, a change in skin temperature, and significantly diminished or absent dorsal foot and posterior tibial artery pulses [2]. In the late stages, fascial compartment syndrome or venous gangrene may develop due to the rapid infiltration of significant bodily fluids into the affected limb. The incidence of venous gangrene caused by PDC ranges from 40% to 60%, while the mortality rate ranges from 20% to 40% [3]. Most critically ill patients in ICU (Intensive Care Unit) suffer from various cardiac and vascular basic diseases and often have a significantly lower quality of life and activity than before the disease, which results in being bedridden for a long time, having tumor base and hypercoagulable blood, and thus prone to lower limb deep vein thrombosis.

2. Clinical Information

The patient, a 68-year-old female, was admitted to the Department of Oncology on 16 February 2022 at 13:06 due to "edema of both lower extremities worsened

for more than one month". She was admitted as a patient with an unknown cause of swelling of lower extremities to the outpatient clinic when she developed edema in both lower extremities over the course of six months that worsened in a recent month. She had an appendectomy more than 50 years ago. In 2008, she was diagnosed with endometrial cancer and underwent total excision of her uterus and ovaries and lymphatic dissection in an outside hospital with postoperative chemotherapy radiotherapy, followed by gradually developed symmetric non-sunken edema of both lower extremities. She was identified as having "bilateral lower extremity lymphatic vessel obstruction." She manifested anaphylaxis as a result of his sulfonamide allergy.

At admission: Examination suggests severe sunken edema of both lower extremities. One day after admission, the patient developed impaired consciousness, opened his eyes, did not respond to calls, did not respond to painful stimulation, and was unable to cooperate with physical examination, flexion and tonicity in both upper limbs and shortness of breath. She had rapid respiration, increased heart rate, decreased oxygenation, a coma-like state, open mouth breathing, double eye gaze, pupils that were the same size and round, measuring approximately 5 mm in diameter, coarse breath sounds in both lungs, no rales were heard, abdominal pressure pain, no rebound pain, and muscle tension. The skin of the right lower extremity was pale, whereas the skin of the left lower extremity was dotted with cyanotic petechiae; the right pathological sign was positive. CT of both lower extremities was subsequently performed on February 17 and February 18, as shown in Figure 1 and Figure 2.

Examination: Blood cell count: white blood cell count: 8.74 * 10^9/L; neutrophil ratio: 95.2%; hemoglobin: 70 g/L; erythrocyte pressure volume: 22.9%; ultrasensitive C-reactive protein: 278.7 mg/L. Blood gas analysis reveals the following values: pH 7.54, partial pressure of carbon dioxide 20 mmHg, partial pressure of oxygen 203 mmHg, bicarbonate concentration 17.1 mmol/L, and lactate 4.0 mmol/L. 18.036 ng/mL mmol/L calcitoninogen, −4.1 mmol/L buffered base, and 4.0 mmol/L lactate. Calcitoninogen 18.036 ng/mL Coagulation: PT: 13.9 S, fibrinogen concentration 7.24 g/L.

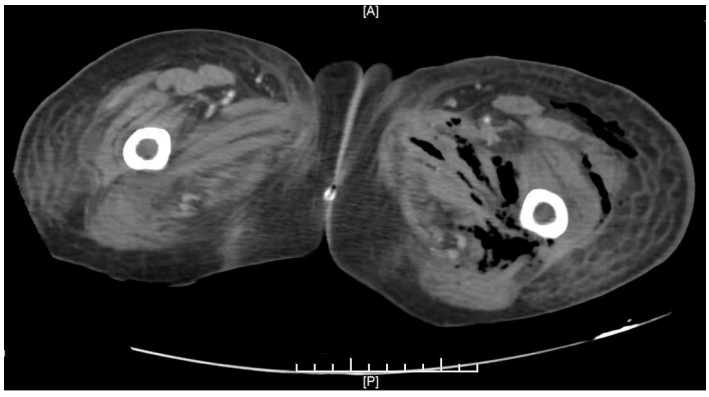

Figure 1. February 17 CT: left common iliac artery aneurysm thrombosis, significant edema, and pneumatization of soft tissues around the left hip, buttock and thigh.

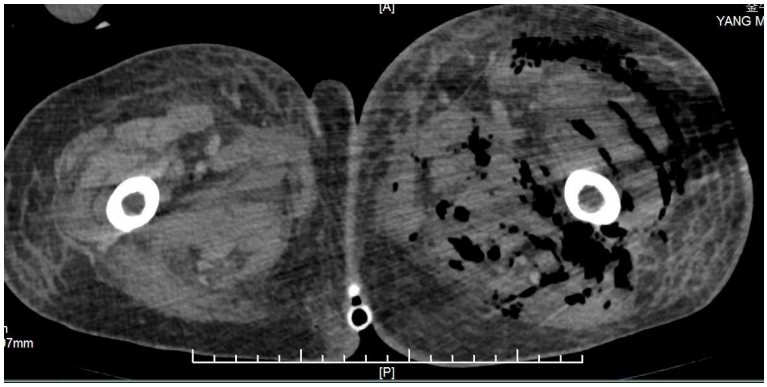

Figure 2. CT on February 18: Significant edema and pneumatization of soft tissues around the left hip, buttock, and thigh, progressing from the previous.

Lower extremity arterial and venous ultrasound: left femoral vein, left superficial femoral vein, left deep femoral vein, and left popliteal vein thrombosis. The fluid of the blister of the skin of the left lower limb was extracted under aseptic conditions with an empty needle and sent for examination: no bacterial growth and no pseudo microbial growth.

After admission, the patient was treated with anti-infection, and anticoagulation therapy was started after the exclusion of bleeding tendency, with comprehensive treatment including monitoring of organ functions, blood transfusion to correct anemia, nerve nutrition, maintenance of internal environmental stability, and nutritional support was given. Collaborative treatment with neurology, orthopedics, interventional medicine, and dermatology was also requested. On the 18th of February, the patient experienced blood pressure and oxygenation decreasing, and she became increasingly unconscious. At this time, she was intubated with an invasive ventilator to assist ventilation and vasoactive drugs to maintain organ perfusion. At this time, the asymmetric swelling of the patient's lower limbs was progressively aggravated, with tension blisters, bruised skin, and an obvious twisting sensation on pressure (**Figures 3(a)-(d)**). The dorsalis pedis artery cannot be located, the blood supply to the toe was very poor, and a comprehensive multidisciplinary evaluation recommended lower limb amputation or interventional revascularization surgery. The family eventually gave up the relevant surgery and all resuscitation treatment due to personal objective factors, and the patient eventually died. Diagnosis at time of death: endometrial cancer (TxNxM0), epilepsy, metabolic encephalopathy, venous thrombosis of the lower extremity (left lower extremity), PDC, iliac artery aneurysm embolism, peritonitis, and sepsis.

3. Literature Review

The author used "PCD" as the keyword to search the Chinese and foreign- related literature published from January 2010 to July 2022 in CNKI, Wanfang Data, and PubMed databases and discovered that the vast majority of them, approximately 93, were case reports. There were 34 retrospective analyses but very

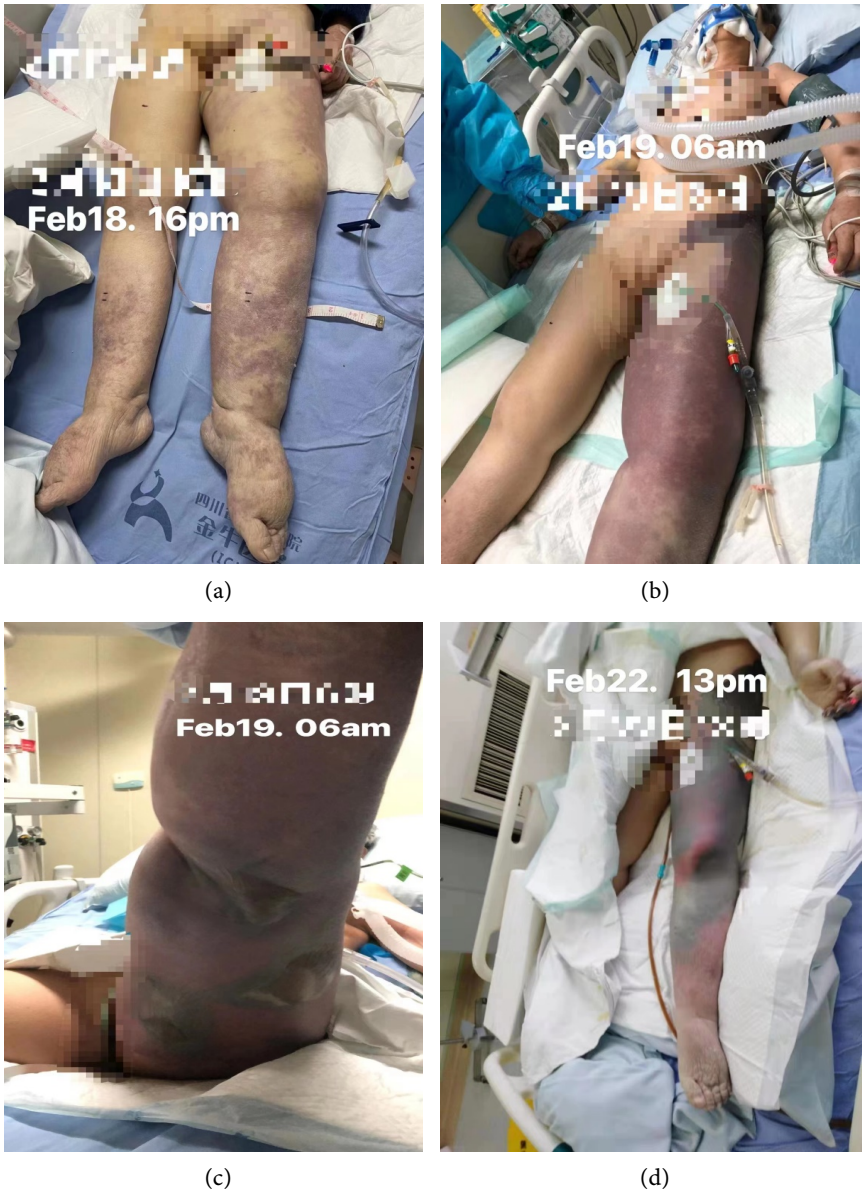

Figure 3. (a)-(d) The patient's left lower extremity skin progressed from Feb. 18 to Feb. 22 which was progressively aggravated, with tension blisters, bruised skin, and an obvious twisting sensation on pressure.

few systematic reviews or multicenter studies. The author provided a general overview of the pertinent PCD examinations, diagnostic criteria, and treatment progress based on the literature review.

PCD, also known clinically as blue phlebitis, is a condition characterized by deep vein thrombosis in the lower extremities accompanied by arterial spasm, resulting in impaired blood circulation in the lower extremities [5]. In most instances, the lower extremity is affected, and cancer is the most common cause. It should be suspected and confirmed by Doppler ultrasound when the classic triad of pain, edema, and cyanosis is present [6]. Color Doppler ultrasound is a safe, non-invasive, and cost-effective method for examining the diseased vessels of a

patient; however, it does not provide a visual, comprehensive, and three dimensional examination of the diseased vessels and is, therefore, less reliable. Digital angiography is the gold standard for the clinical diagnosis of patients with vascular disease, providing more explicit images and more comprehensive data, but it can be traumatic for the patient and requires a higher level of operator skill; multilayer spiral CT can determine deep vein thrombosis based on the filling defect in the venous lumen, and it can also perform three-dimensional vascular reconstruction to show the severity of the affected veins, the collapsing veins, and the occlusions [6].

There is no standard treatment protocol for PCD [1], no randomized controlled clinical trials of significant PCD cases, and no definitive treatment guidelines. The treatment principle should be early anticoagulation to resolve venous reflux and limb hypertension as soon as possible; otherwise, up to 80% of patients will develop post-thrombotic syndrome (PTS), limb amputation, or even death. Currently, the most common interventions are surgical thrombectomy or PMT (percutaneous mechanical thrombectomy), CDT (catheter-contact thrombolysis), and fascial ventriculotomy decompression [1]. Due to the critical condition of patients with femoral cyanotic lower extremity DVT and the extent of the involved thrombosis, there is a high risk that the thrombus will not be removed cleanly during surgery, thereby increasing the likelihood of postoperative complications such as pulmonary infarction. With the improvement of the inferior vena cava filter placement method, however, the safety and efficacy of the procedure have been significantly enhanced, and the incidence of complications such as misplacement, displacement, and perforation during the procedure has been significantly decreased. Patients suffering from femoral cyanotic lower extremity deep vein thrombosis must have an inferior vena cava filter inserted. Thrombolytic therapy was administered to the patient after surgery, and the residual thrombus was dissolved; this effectively compensated for the incomplete removal of the thrombus during surgery and decreased the likelihood of thrombus recurrence after surgery [6]. In addition, the author conducted a national and international review of the relevant literature and discovered that Said A *et al.* queried the electronic medical record database of Beaumont Health *et al.* of patients with PCD hospitalized between July 2009 and November 2019 and discovered that one-third of patients who underwent catheter-only thrombolysis or percutaneous thrombolysis required amputation. Mortality was most significant with percutaneous embolization alone (66%) and lowest with pharmacological, mechanical catheter thrombolysis alone (50%). Percutaneous intervention has become the mainstay of PCD treatment, as evidenced by this large retrospective study and supported by a review of the literature [7]. In 2012, Meissner MH conducted a randomized clinical trial that established non-isolated or low molecular heparin anticoagulation in combination with warfarin as the standard of care for acute deep vein thrombosis (DVT). This treatment is highly effective in preventing the recurrence of venous thromboembolism with a low risk of bleeding but offers only partial protection against the development of the post-

thrombotic syndrome. Early thrombus removal strategies include surgical venous thrombectomy, catheter thrombolysis, and pharmacologic mechanical thrombectomy, with the objective of decreasing the incidence of post- thrombotic syndrome by restoring venous patency and preserving valve function. Although clinical judgment and consideration of individual patient medical conditions and values are required, early thrombus removal strategies should be considered in patients with edema, cyanosis, and acute iliofemoral thrombosis for the first 14 days or less [8]. Mühlberger D *et al.* published a paper on 17 patients with PCD treated with multimodal venous recanalization in 2020, concluding that early recanalization and restoration of venous outflow are necessary for success. Highly urgent surgical embolization combined with multimodal endovenous strategies may be a viable treatment option [9]. In conclusion, the treatment strategy for femoral bruising varies from individual to individual. The appropriate anticoagulant medication should be used along with assessment and staging of femoral bruising according to severity to determine the most appropriate surgical option soon as possible.

Phlegmasia alba dolens (PAD) and phlegmasia cyanosis (PCD) are less common complications of the spectrum of deep vein thrombosis, with a higher incidence of mortality and limb loss. Phlegmasia (mucinosis) is a term used to describe extreme cases of lower extremity deep vein thrombosis that may progress to severe limb ischemia and possible amputation. Fabricius Hildanius first described the disease in the 16th century. In 1938, Gregory coined the term "phlegmasia cerulea dolens," which translates to "painful blue swelling." which translates to "painful blue inflammation" and contrasts with the more common "phlegmasia alba dolens" or "painful white inflammation." This condition is distinguished from the more common "phlegmasia alba dolens" or "painful white inflammation." Femoral leukomalacia, also known as "breast leg," refers to the earliest stages of the condition, during which arterial inflow is compromised due to an extensive thrombotic burden. PCD is a subsequent progression and a precursor to venous gangrene [10]. PCD infrequently occurs in the upper extremity compared to the lower extremities. Greenberg *et al.* reported a PCD of the upper extremities and analyzed data from 37 cases of PCD published in PubMed. It occurs three times more often in the left lower extremity than the right lower extremity and is typically associated with a hypercoagulable state, particularly cancer [11]. Primary risk factors for the development of PCD include hypercoagulability, congestive heart failure, pregnancy, and prolonged immobility. Other factors, such as anatomical abnormalities, a history of previous DVT, previous femoral vein placement, or surgical procedures involving the affected limb, can be highlighted locally [8].

Risk factors for the development of deep vein thrombosis (DVT) to PCD include malignancy, other hypercoagulable states, inferior vena cava filters, previous deep vein thrombosis, contraceptive medications, venous stasis, and trauma, with malignancy being the most prevalent, with an incidence of 33% in one study [12], followed by other hypercoagulable states and inferior vena cava fil-

ters. Chang G. and Yeh J. J. published an article in 2014 suggesting that venous thromboembolism may be the initial manifestation of cancer and may precede the cancer diagnosis in months or years [13]. Early detection and treatment of the underlying malignancy may alter the natural history of venous thromboembolism and reduce the likelihood and incidence of peripheral vascular disease. It is more likely that the left leg will be affected than the right. In 40% to 60% of cases, PCD advances to venous gangrene, which has a 25% to 40% mortality rate and an amputation rate of 12% to 25% in survivors. PCD is classified according to its severity as uncomplicated, adventitious venous gangrene, and venous gangrene [10]. Currently, the three most critical pathophysiologic factors for DVT formation are venous wall injury, venous blood flow stagnation, and blood hypercoagulability [14]. The hypercoagulable state of blood is required for thrombosis, and this hypercoagulable state is linked to the proliferation and metastasis of tumor cells in a vicious circle [15]. Literature indicates that the majority of patients with tumor coagulation thrombosis experience symptoms 3 - 6 months after diagnosis, postoperatively, or after chemotherapy and that the highest incidence of thrombosis occurs after tumor diagnosis and within one year of antitumor therapy [16].

Critically ill patients often have multiple PCD susceptibility factors such as hypercoagulation, heart failure, and trauma, which is a rare condition leading to severe limb ischemia, caused by early arterial flow obstruction secondary to extensive deep vein thrombosis [17]. Subsequently, the author searched through Pub again with the keywords "Intensive Care Unit, phlegmasia cerulea dolens", which only found a few related articles mentioning that COVID-19 infection was associated with the onset of the disease, which was linked with significant venous thromboembolism after neocoronavirus infection [18] [19]. Carey M *et al.* also reported a case of a 58-year-old woman who developed delayed left lower extremity femoral bruising 8 weeks after coronavirus infection, leading to severe complications [19]. The author also searched through China National Knowledge Infrastructure and Wanfang with the keywords "neocoronavirus PCD" and "COVID-19 PCD" and found that there is no such literature issued in China yet.

Based on this, the author used "Tumour," "Venous thromboembolism," "Anticoagulant drugs," "Cancer," etc. as keywords in the research progress of anticoagulant drugs for the prevention and treatment of VTE in CNKI, Wanfang Data, and PubMed for relevant literature published between January 2010 and May 2020.

Commonly used anticoagulants: 1) UFH exerts its anticoagulant effect primarily via interaction with antithrombin III (ATIII). It is ineffective when administered orally and must instead be administered intravenously or subcutaneously. The advantages are rapid onset of action, short half-life, and rapid plasma clearance; the disadvantage is that the activated partial thromboplastin time (APTT) must be monitored during treatment in order to adjust the dose, and the optimal dose is 1.5 to 2.5 times the normal APTT [16]. In addition, a small number of

users (0.2% to 2.7%) may experience heparin-induced thrombocytopenia (HIT), an antibody-mediated adverse reaction that ultimately results in depleted thrombocytopenia and a severe thrombotic state. 2) Low Molecular Weight Heparin (LMWH), LMWH has a significant and long-lasting antithrombotic effect through binding to ATIII and its complex and increases the inhibition of anticoagulant factors Xa and IIa. As a result of the drug's ability to strongly inhibit the activity of anticoagulant factor Xa and weakly inhibit antithrombin (anticoagulant factor IIa), it poses a reduced risk of bleeding while exerting antithrombotic effects. Additionally, the LMWH halflife is increased to 4 h. (1 h for UFH). Moreover, its enhanced anticoagulant effect, simple absorption by subcutaneous injection, and lack of monitoring of APTT or international normalized ratio (INR) make LMWH highly valued in the prevention and treatment of thrombosis [20]. In addition, the reversal agent for both LMWH and UFH is fisetin, which binds to the strongly acidic heparin to form an inactive and stable complex, rendering it incapable of anticoagulation. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend dalteparin sodium as the preferred parenteral anticoagulant for patients with gastric or gastroesophageal lesions, followed by enoxaparin sodium. 3) Factor Xa inhibitors are new oral anticoagulants, *i.e.*, non-vitamin K antagonists (NOACs), that can inhibit prothrombin activity and prolong clotting time by selectively binding to the active site of factor Xa to prevent the interaction between the active site and the substrate [21]. The NCCN guidelines rank apixaban and edoxaban higher than rivaroxaban for the treatment of VTE in oncology patients. Moreover, Garca-Fernández-Bravo I *et al.* published in Blood Res in 2018 the report of a case of cancer-related PCD treated conservatively with direct oral anticoagulants (DOAC), which demonstrated an excellent clinical response, including regression of edema, without bleeding or recurrence of venous thromboembolism (VTE) during follow-up additional complications in terms of [22]. Overall, factor Xa inhibitors have a rapid oral onset of action, fewer interactions with food and commonly used drugs, no monitoring of routine coagulation indicators, and slight individual variation in dose, requiring only a fixed dose, which is convenient for both physicians and patients and is now one of the preferred drugs for the treatment and prevention of VTE [22]. 4) Dabigatranate, the first NOAC to be approved, is a direct thrombin inhibitor that is competitive, selective, and reversible. When apixaban and edoxaban are not indicated for the treatment of VTE in oncology patients, NCCN guidelines recommend dabigatran as an oral anticoagulant [23]. In addition, the specific reversal agent for dabigatran is daclizumab, a monoclonal antibody fragment that binds free and thrombin-bound dabigatran with 350-fold higher affinity than dabigatran, inhibiting the anticoagulant effect of dabigatranate [24]. The chemical structure of warfarin, an oral anticoagulant of the coumarin class, is similar to that of vitamin K. It can inhibit vitamin K-involved coagulation. It prevents blood clotting by inhibiting the synthesis of coagulation factors II, VII, IX, and X [21]. Despite being comparable to oral factor Xa inhibitors in terms of anticoagulant efficacy [25], the NCCN guidelines do not rec-

ommend warfarin as the drug of choice due to the inconvenience of its utilization [11]. However, warfarin is still a good option if patients are more concerned with their finances [26] [27].

4. Conclusion

In summary, it is important to remain vigilant for the occurrence of this complication when diagnosing DVT. Early diagnosis of PCD can be obtained through the use of ultrasound, CT, MRI, and arterial and venous angiography. Careful consideration should be given when selecting anticoagulant drugs. With adequate anticoagulation, a multidisciplinary approach involving orthopedics and interventional medicine should be taken to efficiently carry out the best surgical treatment plan for the patient, particularly for those who are critically ill and also have PCD. This will ultimately increase the patient's chances of survival.

Author Contributions

ZQ and CL were involved in the conception and design of the work. ZQ wrote the first draft of the manuscript and revised it. CL revised the manuscript. YL and ZQ were responsible for the management of this patient, for collecting the clinical data, and for reviewing the literature throughout this study. All authors contributed to the article and approved the submitted version.

Consent

Informed consent has been obtained from the patient's family.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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