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PHLEGMASIA ALBA E CERULEA DOLENS

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Abstract: Phlegmasia alba dolens and phlegmasia cerulea dolens are uncommon conditions that result from acute massive venous thromboembolism. These conditions are associated with lower extremity deep vein thrombosis and have high associated morbidity and mortality. Early diagnosis is essential to reduce overall morbidity and mortality and treatment must be carried out in a timely manner. This activity describes the clinical manifestations and management of Phlegmasia alba dolens and Phlegmasia cerulea dolens and highlights the importance of timely diagnosis by the interprofessional team in the care of patients with these diseases. If patients experience pain, limb swelling, skin changes or discoloration, or motor and/or sensory loss in the context of the aforementioned risk factors, they must seek prompt medical evaluation with concern for deep vein thrombosis.

Keywords: Phlegmasia alba dolens, phlegmasia cerulea dolens, medical research.

INTRODUCTION

Understanding how to accurately and effectively diagnose Acute Venous Thromboembolism (VTE) remains the main focus in hospitalized patients, as VTE sequelae, including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), are among the most common preventable causes. hospital deaths, and their complications are a source of substantial long-term morbidity (JIMENEZ et al. 2021). Phlegmasia Alba Dolens (PAD) and Phlegmasia Cerulea Dolens (PCD) are less frequently encountered complications in a DVT spectrum with a high incidence of mortality and limb loss (GROSS et al. 2021).

Phlegm is a term that has been used to describe extreme cases of lower limb DVT, which can progress to critical limb ischemia and potentially limb loss. This entity was first described by Fabricius Hildanius in the 16th

century and then in 1938 it was Gregoire who coined the term PCD, translated as "painful blue inflammation", differentiating it from the more commonly seen PAD or "white painful inflammation". (HASEGAWA et al. 2008; TURNER et al. 1952). PAD, also known as "milk leg", refers to the early stages of this process due to compromised arterial inflow secondary to extensive clot load. PCD is a more advanced progression and is a precursor to venous gangrene.

GOALS

- Describe the pathophysiology of PAD and PCD.
- Describe the typical presentation and assessment of PAD and PWD.
- Review management considerations for patients with PAD or PCD.
- Summarize the importance of collaboration and communication among the interprofessional team to ensure early diagnosis and prompt therapeutic intervention to improve outcomes for PAD and PWD affected patients.

DEVELOPMENT

ETIOLOGY

The underlying pathological condition of Phlegmasia Dolens is extension of acute VTE that occludes venous flow from one end. The lower extremities are more commonly affected than the upper ones. In the lower extremities, the iliofemoral segment is almost always involved and occluded. In 20% - 40% of cases, phlegmasia was associated with malignancy. However, other risk factors for VTE include hypercoagulable disorders, venous stasis or insufficiency, May Thurner syndrome (compression of the left iliac vein by the superimposed right iliac artery), surgery, trauma, pregnancy, IVC filter placement, use of hormone therapy or oral contraceptives, prolonged immobilization, inflammatory bowel disease, heart failure, and central venous catheterization. In approximately 10% of cases, the etiology remains unknown (SUKOVATYKH et al. 2021; SUCIADI et al. 2021; VYSETTI et al. 2009; TURNER et al. 1952).

EPIDEMIOLOGY

PAD and PDC have been identified as a spectrum of diseases associated with acute massive VTE, the exact incidence being difficult to predict due to the rarity of the disease process. The highest incidence of patients occurs in the 5th and 6th decades of life, but ischemic venous thrombosis has been reported from 6 months to the 8th decade of life. It has a slightly greater predominance in men versus women (SILVA-RODRÍGUEZ et al. 2020; ŞAŞKIN et al. 2017).

Most cases involve the lower extremities, with the left limb more frequently affected than the right due to the anatomical relationship between the right iliac artery superimposed on the left iliac vein; however, it is not uncommon for both lower extremities to be involved. Given the involvement of the iliofemoral segment, PDC is associated with significant post-thrombotic morbidity and high rates of recurrence if not adequately treated (MUACEVIC et al. 2021; VYSETTI et al. 2009). If symptoms progress to venous gangrene, the risk of amputation will be between 20%-50%, with a high mortality rate of 20% to 40%.

PATHOPHYSIOLOGY

PDC is characterized by thrombosis of the deep venous system with permeability of collateral veins and absence of limb ischemia. PCD is a progression of DBP in which there is near-total occlusion of the main deep venous system as well as most of the microvascular collateral veins of the extremity, causing severe venous congestion. The potential window for

reversibility is what differentiates PDC from venous gangrene, in which there is complete obstruction of venous flow to the limb, including extensive and irreversible capillary involvement and often full-thickness necrosis (LIPE et al. 2017; MAITI et al. 2016).

Increased venous hypertension due to venous outflow occlusion results in a change in the pressure differential between hydrostatic and oncotic pressure that leads to increased interstitial edema and massive sequestration of fluid into the limb. The increase in interstitial and compartment pressure leads to collapse of the arterial system as compartment pressure overcomes arterial wall tension. This leads to acute ischemia and venous gangrene. Due to the spacing of the fluid third, hemodynamic instability and hypovolemia occur, increasing patient morbidity and mortality (JIMENEZ et al. 2021; LIPE et al. 2017).

HISTORY

PAD, historically known as "milk leg," presents with the classic triad of swelling, pain, and whitening, with no signs of cyanosis or tissue involvement. The onset of symptoms is unpredictable. They can be gradual over days or fulminant with severe progression over a matter of hours. In 50% to 60% of patients, PAD will precede PDC (GOLEMI ET AL. 2019; FONG ET AL. 2018).

PDC similarly presents with pain and massive swelling due to fluid sequestration. Its most pathognomonic feature is the presence of cyanosis. As cyanosis and worsening venous congestion progress, patients will develop skin changes such as blisters and necrosis and ultimately may experience paresthesia and motor weakness if the edema causes severe arterial compromise and compartment syndrome. Cyanosis begins peripherally, where it remains most intense, but can spread to involve the entire extremity. Gangrene develops in about half of patients with PDC. In 10% to 20% of patients, it remains superficial with preservation of arterial inflow. However, in more severe cases of venous gangrene, deep musculature will be involved and arterial pulses will be absent.

Although much less common, upper limb phlegm has been reported with the presence of ischemic venous thrombosis and gangrene. At least two of the following symptoms have been associated with upper limb involvement: hemodynamic compromise secondary to impaired cardiac output, central vein occlusion or thrombosis often associated with central venous catheterization, and peripheral vein occlusion (GROSS ET AL. 2021; HASEGAWA ET AL. 2008).

Pulmonary embolism is another clinical manifestation of phlegmasia, as the disease process is highly emboligenic and has been shown to have an increased incidence when tissue necrosis is present (DE DONNO ET AL. 2021; ELSAID ET AL. 2019). A high index of suspicion must be present for patients who have clinical symptoms of DVT and associated tachycardia or significant oxygen requirements.

EVALUATION

A significant part of the diagnosis of DVT and phlegm is made clinically with a focused history and physical examination, including details about the onset and duration of symptoms, functional impairment related to the compromised limb, comorbidities, previous venous or arterial interventions, and personal or family history. thrombophilia or hypercoagulability. A complete pulse examination of the proximal and distal pulses at the extremities must be performed to assess arterial inflow. Edema can often make this challenging, and a Doppler may be needed to assess intact signs. If blisters or skin necrosis, arterial or neural involvement, or venous gangrene are present at presentation, this is

considered emergent, and immediate, limb-threatening efforts must be undertaken to remove the thrombus and increase venous return.

Laboratory investigation must include a complete blood count, standard coagulation profile (international normalized ratio, platelets and partial thromboplastin time) and a basic metabolic panel to assess renal function and hydration status.

The gold standard for confirming the diagnosis of DVT is contrast venography; however, this is not clinically practical. Instead, venous duplex ultrasound has replaced contrast venography as the preferred imaging modality for diagnosis. Magnetic Resonance Venography (MRI) or Computed Tomography Venogram (CTV) are alternative diagnostic studies that are particularly useful in visualizing proximal thrombus in the iliac veins or VTC and in identifying anatomical abnormalities in the pelvis causing compression of the iliac vein. However, both imaging modalities have disadvantages. MRV is time-consuming compared to CT and may be limited by motion artifact in patients who experience acute, severe pain. CT inherently exposes the patient to radiation, but also poses the threat of nephrotoxicity with the use of iodinated contrast, particularly in a subset of patients who may be critically ill and in hypovolemic shock.

Alternatively, patients who are candidates for catheter-based intervention may have venography performed at that time to further assess the extent and nature of the thrombus and to guide further management.

Sonographic features suggestive of DVT on ultrasound are lack of compressibility, absence of spontaneous flow through the vessel, increased vein diameter, and increased echogenicity present in the vessel lumen.

TREATMENT

There has been variability regarding the management of acute DVT with associated phlegmasia or gangrene. The mainstays of treatment are to prevent the spread of intravenous coagulation and further stasis, reduce venous hypertension, avoid hypovolemic shock with fluid resuscitation, prevent progression to fulminant gangrene, and preserve tissue viability and treatment of the underlying disease, 2021; DEKKERS et al. 2017).

Supportive measures must be taken immediately and are considered first-rate. The extremity must be elevated to an angle greater than 60 degrees above the level of the heart to avoid venous stasis and increase venous return through the remaining patent channels. Failure to achieve significant elevation may be responsible for progression to venous gangrene. Elevation will also reduce edema and compression in the arterial system, preventing circulatory collapse and hypovolemic shock. Historically, other supportive treatments including hot compresses, sympatholytics, anti-ospastic drugs, and steroids have been advocated. However, they have shown little or no benefit and are not currently recommended (BARNETT et al. 2020; FONG et al. 2008; CHAOCHANKIT et al. 2018).

Definitive management involves anticoagulation, catheter-directed thrombolysis, thrombectomy, or any combination of the three, depending on the severity of the presentation. Most patients will respond to treatment with fluid resuscitation, aggressive elevation, and anticoagulation. Intravenous unfractionated heparin must be administered immediately as a bolus dose of 10-15 units/kg and then continued as an intravenous infusion being titrated to a therapeutic active partial thromboplastin time (aPTT) of 1.5 to 2 times the value. of laboratory control. Patients who have

advanced PDC or venous gangrene or those with refractory venous thrombosis on anticoagulation may be considered for catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy, or open surgical thrombectomy (MUACEVIC ET AL. 2021; GOLEMI ET AL. 2019; VYSETTI ET AL. 2009).

Before the advent of endovascular intervention, open surgical thrombectomy was the treatment of choice over emergency intervention. This is associated with high rates of recurrence and vessel-related complications, such as endothelium denudation, rupture, intimal hyperplasia, and low clinical durability. TDC, on the other hand, allows for less mechanical trauma to the vessel and has become preferred over open surgical thrombectomy in patients who are candidates for lysis. In addition, it allows for potential recanalization and elimination of thrombus from smaller venules that open surgery cannot access. Using this technique, thrombolytic agents are infused directly into the venous system through a multi-hole infusion catheter, allowing for dissolution of a thrombus in small distal and collateral vessels not accessible to a balloon embolectomy catheter. Heparin is infused simultaneously at a subtherapeutic rate (300 to 500 IU/hour) to prevent catheter thrombosis and fibrinolytic is infused into the target area for up to 48 hours. The most common agent used with TDC is tissue plasminogen activator (tPA), and the usual dose is 0.5 mg to 1 mg/hour. The degree of swelling, as well as pulses, must be routinely assessed, and clotting factors must be monitored with serial laboratory extractions to ensure close monitoring, given the increased risk of bleeding.

The clinical efficacy of TDC has been proven in several studies demonstrating that patients with symptomatic iliofemoral DVT had significant clinical improvement with a rapid reduction in thrombus load, restoration of luminal patency, and a decreased risk of valve dysfunction and postthrombotic syndrome (DE DONNO ET AL. 2021; GOLEMI ET AL. 2019; CHAOCHANKIT ET AL. 2018; HASEGAWA ET AL. 2008). As with any fibrinolytic treatment, it carries a risk of bleeding complications, the most serious being intracranial hemorrhage. In addition, it is less successful in patients with subacute or chronic symptoms with a duration of symptoms longer than 10 to 14 days.

Contraindications for lysis therapy include: Absolute contraindications, Active bleeding or bleeding diathesis (excluding menstruation), Closed head/facial trauma or stroke within 3 months, Recent neurological surgery, Coagulopathy, Intracranial vascular injury or malignant or recent spinal surgery, Previous intracranial hemorrhage, Relative contraindications, Surgery within the last 10 days, Severe uncontrolled hypertension at presentation, Recent trauma or gastrointestinal bleeding or active peptic ulcer, Severe liver or kidney disease, Traumatic or prolonged CPR, Current anticoagulant use with INR > 1.7 or PT > 15s and Pregnancy (ELSAID ET AL. 2019; HASEGAWA et al. 2008).

Percutaneous mechanical thrombectomy (PMT) has also proven to be an effective alternative or adjunctive therapy to DTC using a mechanical thrombectomy catheter that aspirates or macerates the thrombus. There are several catheter-directed techniques for mechanical thrombectomy and manual thrombus extraction, including rheolytic, rotational, aspiration, and angioplasty. Comparing PMT with CDT, PH Lin et al. reported advantages of PMT such as shorter thrombolytic infusion time compared to DTC alone and lower risk of bleeding. In addition, they found that there were significantly shorter ICU stays, as well as shorter hospital stays and

the need for fewer venograms (JIMENEZ et al. 2021).

In addition to bleeding complications, in patients undergoing BDT or MRV, there is also a risk of pulmonary embolism. Lysis can cause clot fragmentation and manipulation of wires in the veins can dislodge the thrombus. Given this concern, consideration must be given to placing an IVC filter in selected patients with extensive load that extends into the IVC. Recently, a randomized controlled trial FILTER-PEVI (filter implantation to decrease thromboembolic risk in percutaneous endovascular intervention) demonstrated an eight-fold increase in symptomatic iatrogenic PE in patients who did not receive a filter before the intervention. However, mortality was not different in those without a filter compared to individuals who had a filter in place (SUCIADI ET AL. 2021; LIPE ET AL. 2017; MAITI ET AL. 2016).

As mentioned earlier, open surgical therapy is performed infrequently. Venous thrombectomy in the form of open exposure followed by passage of a proximal and distal Fogarty balloon catheter has historically been performed. Other more involved procedures have also been described, such as transabdominal cavotomy and thrombectomy, but also more frequently performed before the advent of percutaneous endovascular therapy and no longer have a role in the treatment of PCD and venous gangrene. Overall, they have been shown to decrease the risk of fatal and non-fatal pulmonary embolism; however, the procedure itself is very morbid.

Although not often found in patients who present with phlegmasia and venous gangrene, compartment syndrome must always be considered. If there is any doubt after restoration of arterial inflow and venous outflow to the limb, a four-compartment fasciotomy to prevent muscle necrosis must be performed. If amputation is necessary because initial efforts with fasciotomy have failed, it is recommended that this be delayed, if possible, to give the limb time to demarcate and the swelling to improve.

DIFFERENTIAL DIAGNOSIS

- Arterial embolism
- Deep vein thrombosis
- Cellulitis
- Lymphedema
- Venous valve insufficiency
- Superficial thrombophlebitis

PROGNOSIS

The overall prognosis remains relatively poor and worsens as symptoms progress. Overall mortality varies from 20% to 40%, especially if there is gangrene (SUCIADI et al. 2021; MUACEVIC et al. 2021; GROSS et al. 2021).

Despite prompt treatment in patients who develop acute DVT or phlegm, a significant percentage of patients will develop venous valve regurgitation and post-thrombotic syndrome. Valve incompetence has been reported in up to 20% and 44% at 5 and 10 years, respectively (SUKOVATYKH et al. 2021).

COMPLICATIONS

- Venous gangrene
- Loss of member
- Pulmonary embolus
- Compartment syndrome
- Post-thrombotic syndrome
- Death

PATIENT EDUCATION

Knowledge of risk factors for the development of DVT is important for early recognition and prevention of symptom progression. The following are risk factors: previous diagnosis of DVT or PE, family history of DVT or PE, hypercoagulable

disorders, diagnosis of venous stasis or insufficiency, May Thurner syndrome (compression of the left iliac vein by the underlying right iliac artery), greater recent surgery, trauma, pregnancy, obesity, use of hormone replacement therapy or oral contraceptives, prolonged immobilization, inflammatory bowel disease, heart failure, and central venous catheterization.

If patients experience pain, limb swelling, skin changes or discoloration, or motor and/or sensory loss in the context of the aforementioned risk factors, they must seek prompt medical evaluation with concern for deep vein thrombosis.

IMPROVING THE RESULTS OF THE MULTIDISCIPLINARY TEAM IN HEALTH

The presence of acute iliofemoral DVT with symptoms of a painful, swollen, cyanotic extremity is consistent with a diagnosis of phlegmasia alba dolens or cerulea dolens. Given its ability to rapidly progress to tissue necrosis and venous gangrene, this is an emergency. It is usually administered by an interprofessional team of healthcare professionals, including a vascular surgeon, a hospitalist, a hematologist if DVT is not provoked, and, depending on the severity, an intensive care specialist. Clinically, it is an easily recognized entity and the diagnosis can be confirmed with venous duplex ultrasound. If diagnosed early, DVT can usually be treated conservatively. However, patients who show signs of phlegmasia cerulea dolens often require more invasive surgical intervention. If there is progression to venous gangrene, it can lead to limb loss and even death. Given this risk, early diagnosis is vital and patient and provider awareness and recognition are essential. Once the diagnosis is confirmed, the patient must be immediately placed on bed rest, fluid resuscitation must be performed, the affected limb must be elevated, and an intravenous heparin bolus followed by infusion must be initiated. 2020; GOLEMI et al. 2019).

Institutional resources and specialist experience must be taken into account when determining the management of PCD and venous gangrene. Ideally, a vascular surgery or interventional radiology appointment must be obtained to assess and assess the extremity to determine if further intervention is needed. The use of systemic thrombolytic therapy was initially tested but is not recommended for the treatment of DVT and its sequelae due to an increased risk of major bleeding. [Level 1] In appropriate patients, catheter-based thrombolytic therapy or mechanical thrombectomy in combination with systemic anticoagulation has been proven to improve treatment outcomes for patients who have not responded to systemic anticoagulation therapy alone (GROSS et al. 2021; BARNETT et al. 2020; FONG et al. 2018).

In patients with progressive venous gangrene, open surgical thrombectomy can be considered as a first-line intervention to allow rapid removal of the thrombus and restoration of peripheral circulation, particularly if they are not candidates for lysis or endovascular intervention. 2021; MORAES et al. 2021; LIPE et al. 2017).

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