

Incidence and Characteristics of Phlegmasia Cerulea Dolens. A 17-Year, Descriptive Study in a Third-Level Hospital in Madrid

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ABSTRACT

Introduction: Phlegmasia cerulea dolens (PCD) presents initially as a triad of pain in the affected limb, oedema and cyanosis. In more advanced cases, venous gangrene, pre-renal shock, arterial insufficiency, and even death. Study objectives were to ascertain the incidence of PCD in our hospital, to compare our patients' characteristics with those described in the literature and taper of point of care ultrasound in its diagnosis

Material and methods: This was a retrospective, observational, descriptive study. The study period was from July 24th 2002 to April 30th 2019. It was conducted in a third level hospital in Madrid, Spain.

Results: Thirty-three patients were diagnosed with PCD, 21 (63.7%) women and 12 men. Mean and median of age was 72 years. Range was from 38 to 89 years. The main association was with cancer, in 19 patients (57.5%), and pulmonary embolism in 9 patients (30%). Our mortality rate was 24%. The incidence of PCD in our study, is about 1:73,000 patients.

Conclusion: The incidence of PCD in our hospital was 1:73,000. As soon as the clinical suspicion of PCD is raised, early diagnosis and treatment is crucial, with the aim of saving patient's lower limb and life. This is the only point where all publications coincide.

Keywords: Phlegmasia Cerulea Dolens

INTRODUCTION

Phlegmasia cerulea dolens (from Greek φλέγμα, *phlégma*: inflammation, and from Latin *Cerulea*: bluish or cyanotic coloration; *Dolens*: painful) is an infrequent, fulminant type of massive deep venous thrombosis (DVT), that may lead to venous gangrene and death if not early and properly treated. The exact cause of *phlegmasia cerulea dolens* (PCD) is unknown. It can be considered as part of a spectrum, intermediate between *phlegmasia alba dolens* ("painful white inflammation") and venous gangrene. In *phlegmasia alba dolens*, only major deep venous channels of the limb are occluded, while collateral veins are still permeable, i.e., there is no venous congestion, as in PCD.¹ The final stage of the spectrum is venous gangrene, which we should avoid with an early diagnosis and immediate proper treatment.

PCD was first described by Hildanus in 1593.¹ In 1937, Fontaine and deSouza-Pereira¹ showed that complete ligation of the venous circulation in the leg of the dog produced gangrene. In 1937, Grégoire² was the first author to coin the term PCD. It has been described as equally frequent in both sexes, and more frequent between the 4th and 5th decade of life.¹ Factors that predispose to DVT also predispose to PCD^{2,3}: hypercoagulability (procoagulation) conditions,

cancer¹, tobacco, immobilization, diabetes mellitus, etc. In 90% of cases, there is a triggering factor, the main one being malignant pathology¹ (40%).

PCD presents initially as a triad of pain in the affected limb (from mild to severe), oedema (variable degree of swelling) and cyanosis (= venous congestion). In more advanced cases, venous gangrene (when also affects subcutaneous tissue, muscle and skin), pre-renal shock (fluid sequestration), arterial insufficiency, and even death.^{2,3}

Initial clinical diagnosis should be done *de visu* (Figure 1). Diagnosis can be confirmed quickly, as other DVT, with point of care ultrasound (POCUS).⁴⁻⁶ Subsequently, the radiology department could confirm it with Doppler ultrasound. Immediate treatment should be started, as this is essential to save limb function. Complications of PCD are more frequent if treatment is delayed: venous infarction leading to gangrene, limb amputation, pulmonary embolism, post-phlebotic syndrome, fluid sequestration in the affected limb and systemic inflammatory response syndrome (leading to hypotension and shock), arterial insufficiency due to congestion and even death.

The incidence of PCD is not known. The vast majority of PCD's publications in the literature are about case-reports, and all of them agree that PCD is a rare or very rare disease. Nonetheless, despite this rareness, to the best of our knowledge, no studies about its incidence have been published.

MATERIAL AND METHODS

This was a retrospective, observational, descriptive study. We followed the RECORD statement (checklist of items,

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extended from the STROBE statement), commonly used in observational studies using routinely collected health data. The study was performed in University Hospital “Ramón y Cajal”. This is a third level hospital in the province of Madrid (Spain) where all surgical procedures are available, including transplants.

The study included person-level data and no other data linkage across databases. We reviewed all the clinical histories where PCD was at least one of the diagnoses. In all patients, we collected the following data: sociodemographic characteristics, such as age (in years), sex, race; affected limb; time of hospitalization; associated diseases or conditions: cancer, tobacco, hypertension, diabetes mellitus, hyperlipidaemia, stroke, pregnancy /postpartum, atrial fibrillation, previous immobilisation; associated complications: pulmonary embolism, limb amputation, death; imaging studies: if Doppler ultrasound, POCUS, computed tomographic pulmonary angiography; treatment whilst admitted and treatment of discharge. Whenever any of these data could not be obtained from a patient (lost data or not documented), this is stated in the results.

The study period was from July 24th 2002 to April 30th 2019, i.e., during last 17 years.

The Research and Teaching unit of the Emergency Department of University Hospital “Ramón y Cajal” approved the trial. As no patient’s names and no clinical intervention was performed, this study did not need an approval by the Ethics Committee at our hospital.

The IBM SPSS 20.0 statistical software package was used for all statistical analyses.

RESULTS

We found 33 PCD patients, 21 (63.7%) women and 12 men, all Caucasian. Mean age of patients was 72 years, 74 years in females and 70 years in males (no statistical significance); range was from 38 to 89 years, and the median was 72 years. The main association of these patients was with cancer, in 19 patients (57.5%) (Table 1).

Their location was: left lower limb in 21 patients (64%), right lower limb in 10 patients (30%), in both lower limbs in 1 patient (3%), and finally in left upper limb in 1 patient (3%). Mean of hospitalization was 14 days.

All patients had Doppler ultrasound of their lower limbs. Only 19 patients had POCUS done; nonetheless, they suppose 100% of the patients attended in or after 2010, when this technique was available at our hospital. All PCD were previously diagnosed with POCUS even before going to Doppler ultrasound.

Pulmonary embolism at some time of their hospitalization occurred in 9 patients (30%); this diagnosis was done with computed tomographic pulmonary angiography in 7 patients (23%), and in 2 patients (7%) the diagnosis was clinical. No



Figure-1: Diagnosis *de visu* of phlegmasia cerulea dolens

information could be obtained from 3 patients.

Regarding the treatment, 30 patients (91%) were treated with low molecular weight heparin (LMWH), 2 (6%) patients with unfractionated heparin (UFH) and in 1 patient (3%), the prescribed treatment could not be obtained.

The outcome was satisfactory in 23 patients (69%), 8 patients (24%) died during their hospital admission. In 2 (6%) patients, the outcome was not documented. Regarding the treatment of discharge, 9 patients (27%) were treated with acenocoumarol and 22 (66%) with LMWH, and 2 (6%) patients had no documented treatment.

DISCUSSION

In this 17-year review, with 33 patients diagnosed with PCD, from 2,410,013 emergencies attended in our hospital, the incidence of PCD is about 1:73,000. To our knowledge, this is the first hospital review of the incidence of PCD, so we cannot compare this data with previously published ones.

Of our 33 patients, 21 (63.7%) were women and 12 men. This contradicts other authors, who reported either an equal incidence between sexes¹, or an increased 1.5 males to 1 female ratio.⁷

As in Stallworth’s¹ paper, we did not have any Black ethnic patient in our study. We believe this fact is not significant, as this race is a minority in our environment.

Classically the left lower limb had been described more often than the right lower limb. The explanation for this feature may be that the left common iliac vein can be compressed by the overlying right common iliac artery, thus facilitating a DVT. In our series, the left lower limb was involved in 21 patients (64%), right lower limb in 10 patients (30%), both lower limbs in 1 patient (3%), and finally in left upper limb in 1 patient (3%). Other authors also report PCD more frequently in left lower limb. Nonetheless, bilateral PCD had been reported in large series as frequent as in 26% of patients, in our series, bilateral PCD was only one case (3%). We cannot find any explanation for this.

As in other studies, the main association of PCD patients was with cancer (57%). This is also described by other authors.^{1,3,7}

	Cancer	Tobacco	Hypertension	Diabetes mellitus	Dislipidemia
Number of cases	19	14	13	9	6
Percentage	57%	42%	39%	27%	18%

Table-1: Main association of phlegmasia cerulea dolens with other risk factors

The most severe complication of DVT, also for PCD, is pulmonary embolism. This was diagnosed in 9 patients (30%) in our series, almost same incidence as in other revision (29%).⁷ As per literature, our patients were mainly treated with LMWH. Our 2 patients treated with UFH were from 2002 and 2003. There is no evidence about the usefulness of the new oral anticoagulants, factor Xa inhibitors (rivaroxaban, edoxaban, apixaban) and oral direct thrombin inhibitors (dabigatran) in the treatment of PCD.⁸ Regarding the discharge treatment, patients with acenocoumarol are from the beginning of our search, mainly from 2002 to 2007. Patients from the last twelve years were all discharged with LMWH.

As a curiosity, one patient had PCD from his left upper limb that according to literature is an extremely rare presentation.⁹ We have no evidence, but we have a high suspicion that (as in our patient), peripheral vein access treatments play an important role in PCD of upper limbs.

Regarding the prognosis, 8 patients (24%) died during hospital admission, compared with the available data (31%) from the literature.¹

According to published studies, in more severe cases, surgical treatment of PCD can be needed. It can be an endovascular approach or open surgical thrombectomy. Endovascular targeted thrombolytic therapy is the intervention of choice.¹⁰⁻¹¹

Thrombolytic therapy can be combined with endovascular mechanical thrombectomy. Open surgical thrombectomy should be employed when endovascular approach is not possible.

We can point out that despite being our hospital, a third level one, with all kind of surgeries available, no patient was performed any kind of surgical procedure, neither embolectomy nor amputations. We wonder if early treatment with LMWH could have avoided surgical procedures. Anyway, our mortality rates are similar (even lower) than in other series.

As weak points of our study, we can think, that theoretically, it is possible that its incidence could be higher, because some PCD could have been diagnosed as DVT. In our environment, the prevalence of Black and Asian ethnics are very low, much lower than in the USA and other more industrialized European countries.

We wonder if comparison of PCD incidence among hospitals from different countries and environments, with or without POCUS, will be much different from ours.

Finally, we can only hypothesize that faster diagnosis of PCD with POCUS could had played a role in quicker treatment, and consequently, a better (or least bad) prognosis of our PCD patients.

CONCLUSION

The incidence of PCD in our hospital was 1:73,000. We cannot compare with any other data, as not available.

As soon as the clinical suspicion of PCD is raised, early diagnosis and treatment is crucial, with the aim of saving patient's lower limb and life. This is the only point where absolutely all publications coincide.

The use of POCUS in the emergency department speeds up the confirmatory diagnosis of these patients. Doppler ultrasound performed by radiology department is definitely not needed to start with the medication, but should be requested for full confirmation.

The early initial treatment should be with LMWH, regardless of the surgical decision, leaving the invasive management depending on the patient's condition, the availability of resources and the experience of the surgical team.

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