


Syndromes Associated With the Deep Veins: Phlegmasia Cerulea Dolens, May–Thurner Syndrome, and Nutcracker Syndrome

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Abstract

Although phlegmasia cerulea dolens, May–Thurner syndrome, and nutcracker syndrome are rare entities, knowledge of these syndromes associated with the deep veins is essential. This study presents current management of these disorders, including diagnostic and interventional strategies. Endovascular techniques have evolved and now play a significant role in the treatment of both phlegmasia cerulea dolens and May–Thurner syndrome. However, endovascular therapy for nutcracker syndrome remains untested.

Keywords

deep vein thrombosis, phlegmasia cerulea dolens, May–Thurner syndrome, nutcracker syndrome, fasciotomy, endovascular therapy

Introduction

Significant maladies associated with the deep venous system infrequently present to the vascular surgeon. Nonetheless, disorders such as phlegmasia cerulea dolens, May–Thurner syndrome, and the nutcracker syndrome have a profound impact for patients and require, in some settings, rapid diagnosis and treatment. A thorough understanding of these syndromes and their therapeutic alternatives is important for providing optimal interventional therapies and maximizing outcomes.

Phlegmasia Cerulea Dolens

Phlegmasia cerulea dolens (PCD) is a rare and serious sequela of extensive iliofemoral vein thrombosis.^{1,2} PCD is defined as acute limb ischemia due to total or near total thrombosis of the venous outflow of an extremity.^{2–6} PCD occurs when a large deep vein thrombosis (DVT) creates severe and sudden venous hypertension that leads to tissue ischemia with resultant profound translocation of fluid into the interstitial space.^{3,5,7–9} The natural history of PCD progresses from severe venous hypertension to massive extremity swelling followed by tissue ischemia and ultimately venous gangrene.^{4,5} There is no clear consensus about the pathophysiology of PCD; however, it is

believed that arterial insufficiency occurs as a result of small artery collapse.^{3,5} Venous gangrene, defined as tissue necrosis from complete venous occlusion,^{5,10} occurs in as many as 40% to 60% of PCD cases and is associated with a poor prognosis for survival. Although it is unknown why PCD is so lethal, it is hypothesized that this may be due to dysregulation of homeostasis between coagulation and fibrinolysis as well as circulatory collapse and shock from loss of venous return.^{4,5,11} PCD historically carries a 20% to 40% mortality,^{4,7,12} and the amputation rate has been reported as high as 20% to 50%.^{3,5,10,13} though this has not been reevaluated in the current era. Risk factors for PCD include malignancy, immobility, heart failure, heparin-induced thrombocytopenia (and other prothrombotic states such as antiphospholipid syndrome), pregnancy, surgery, and venous instrumentation including placement of central venous catheters and inferior vena cava (IVC) filters.^{4,5,11,14–17}

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Notably, PCD is distinct from phlegmasia alba dolens or “milk leg” (a moniker denoting the preponderance of postpartum women with this condition). Haimovici¹⁰ described phlegmasia alba dolens as a stage in the thrombophlebitic continuum prior to PCD. Massive thrombosis of the iliofemoral veins with sparing of the venous collaterals defines phlegmasia alba dolens whereby alba dolens does not ultimately result in limb ischemia. Patients typically present with a swollen and painful extremity that blanches, in contrast to PCD where the extremity appears blue and mottled. With phlegmasia alba dolens, unlike PCD, amputation is rarely necessary.^{5,8} Nonetheless, presentation with phlegmasia alba dolens does not preclude development of PCD as up to 50% to 60% of PCD cases are preceded by phlegmasia alba dolens.¹⁸

Clinical Findings

The physical findings of PCD are the basis of its name: severe extremity swelling, cyanosis, and pain in the setting of significant venous outflow obstruction.^{4,5,14} Patients typically present acutely with a tense, mottled, purple extremity. The changes start distally and extend proximally at varying rates. This degree of venous outflow obstruction leads to ischemia, which manifests as unremitting pain. Arterial signals are typically intact though are rarely palpable. Sensory and motor impairment is indicative of imminent venous gangrene and high potential for limb loss.² In addition, the patient with PCD appears gravely ill, showing signs of pronounced volume depletion, including tachycardia, hypotension, and low urine output. This is consistent with the historic reports of up to 6 to 10 liters of interstitial fluid loss within 5 to 10 days.^{5,19}

Patients with PCD are classically female, although men in their fifth and sixth decades can be affected as well. The left lower extremity is the most commonly affected extremity,^{5,6} and up to 5% of PCD cases occur in the upper extremity.^{2,6,20}

Diagnosis

Diagnosis can be made on clinical presentation alone, as nearly all patients present with an ischemic mottled extremity and appear toxic. Another helpful clue is that many of these patients will have a recent diagnosis of DVT.

If there is uncertainty in the diagnosis, Doppler ultrasonography (DUS) may be used as a rapid, inexpensive, and noninvasive way to confirm the diagnosis.⁵ Despite arterial signals, patients with true PCD will demonstrate signs of ischemia, with sensory and/or motor dysfunction.

This is the hallmark of PCD and precludes the need for more extensive imaging. However, if determination of the extent of thrombus is necessary, computed tomographic angiography (CTA) may be used. Magnetic resonance venography (MRV) provides additional confirmation of the diagnosis, if time allows, as it eliminates radiation exposure and does not require the use of nephrotoxic iodinated contrast that can be harmful in the setting of severe volume depletion.

Treatment

Historically, it has been argued that PCD is a terminal event and that therapeutic interventions are futile.^{4,5} Despite this, a number of therapies have been used, including extremity elevation, intravenous heparin, thrombolysis, open thrombectomy, fasciotomy, and amputation. Because of the rarity of this condition, there is no clear consensus for treatment of this potentially lethal disorder, although definitive criteria and guidelines are anticipated in the near future. Regardless, it is essential to recognize that standard treatment for conventional DVT is insufficient for PCD^{4,21} as up to 80% of survivors will develop postthrombotic syndrome and chronic venous stasis changes if the significant burden of venous thrombus is not addressed.²

Intervention is typically multimodal and should be aimed at both preventing progression to venous gangrene by reducing venous hypertension and high interstitial pressures as well as restoring venous outflow to the affected extremity.^{5,14} Initial management of PCD includes aggressive fluid resuscitation, bed rest, and elevation of the affected limb.⁵ Emergent fasciotomy of the calf or forearm to decompress small veins, increase venous outflow, and reduce interstitial pressure is the critical primary intervention necessary to secure limb-salvage for the patient with impending tissue necrosis.^{9,22,23} In some cases, thigh fasciotomy is required as well. These measures are critical to emergent intervention for the patient with severe ischemia as thrombolysis requires many hours to complete during which ischemic tissue can progress to full necrosis.²³

Catheter-directed thrombolysis is an important intervention to preserve long-term function and may be deferred until after the acute event or entirely if the patient has absolute contraindications to thrombolytic therapy. The safety and efficacy of catheter-directed thrombolysis in symptomatic DVT, using local delivery to maximize contact with thrombus while decreasing systemic effects, has been well demonstrated.^{2,21,24} Catheter-directed thrombolysis is associated with complete resolution of thrombi in up to 90% of patients with PCD.^{6,25,26} Venous thrombectomy (with or without

arteriovenous fistula) is reserved for patients who are not candidates for thrombolytic therapy, as the morbidity associated with this procedure is high (including potential damage to valves) and technical success is challenging.² Moreover, open thrombectomy is less effective than thrombolysis, as surgical thrombectomy cannot address the clot in small veins involved in the progression to venous gangrene.⁶

Some authors (including ourselves) advocate placing an IVC filter prior to starting thrombolytic therapy in order to prevent embolization of the significant clot burden. Ideally, an access site remote from the venous intervention, such as a transjugular approach, should be used as it reduces potential complications such as bleeding at the insertion site.^{16,27} The filter should be carefully placed infrarenally, as there is potential for renal vein thrombosis in the setting of PCD, with its severe prothrombotic state that is exacerbated by profound intravascular volume depletion. Filter placement in this setting is not without hazard. Apart from bleeding from the access site, filter placement can also increase the risk of perpetuating lower extremity thrombosis and has been reported to be an inciting event for PCD in patients for whom a filter is placed without concomitant anticoagulation.²⁸

Access to the iliofemoral vein for thrombolysis is typically achieved via the transpopliteal approach. With the patient in the prone position, the popliteal vein can be accessed directly or via the small saphenous vein (SSV). Although cannulating the SSV avoids a potential arterial puncture in the setting of thrombolysis, it can be difficult to navigate the introducer wire through the SSV–popliteal junction when the popliteal vein is thrombosed. With a sheath in the popliteal vein, a catheter can be advanced through the clot and across the iliofemoral thrombus. A thrombolysis catheter can then be placed within the thrombus for infusion of the lytic agent. Forty-eight hours of thrombolytic therapy is typically required (with interval venography) to completely lyse the extensive thrombus associated with PCD. Consideration of percutaneous mechanical thrombectomy is appropriate in this setting. This is discussed more extensively in the subsequent section.

Concern about bleeding while using a combination of thrombolysis and fasciotomy in our experience is unfounded. Because the effectiveness of thrombolytic therapy for PCD is not diminished by waiting 24 to 48 hours, starting thrombolysis in a delayed fashion to ensure that the fasciotomy wounds are hemostatic is possible. In addition, delaying intervention on the deep veins will allow for time to resuscitate the critically ill patient. Nonetheless, the authors have used catheter-directed thrombolytics immediately following fasciotomy without significant hemorrhagic complications.

Immediate postprocedure care includes systemic anticoagulation and elevation of the affected extremity. Care to limit compression of the limb in the acute setting is important in that a modest amount of compression can collapse the small venules decompressed via fasciotomy and potentiate ischemia. Although patients with complete resolution of their venous thrombosis have high potential for full recovery, long-term oral anticoagulation, compression stockings, and physical therapy may be necessary.²⁹

May–Thurner Syndrome

In 1957, May and Thurner³⁰ described this anatomic variation in which venous obstruction of the left common iliac vein was the result of chronic pulsation and compression by the overlying right common iliac artery and underlying lumbar vertebral body. They identified iliac vein spurs in 22% of 430 cadavers and theorized that these were the result of mechanical obstruction by the iliac artery. This mechanical obstruction led to intimal hyperplasia, followed by venous obstruction and an increased potential for thrombosis.³⁰ Today, May–Thurner syndrome is defined as left lower extremity venous hypertension from compression by the iliac artery with or without left iliofemoral DVT.^{31–33}

The prevalence of May–Thurner is unknown, and possibly underestimated, as the majority of patients with iliac vein compression are likely asymptomatic.^{34,35} Both cadaveric studies and retrospective review of computed tomography (CT) images from asymptomatic patients suggest this anatomic variant is present in approximately 22% to 24%³¹ of the population. Nonetheless, Wolpert et al³⁵ report a 37% incidence of left iliac vein compression in patients with left lower extremity swelling, and others hold that May–Thurner is responsible for up to 2% to 3% of all lower extremity DVT.^{36,37}

Clinical Findings

Patients who have clinical symptoms associated with May–Thurner syndrome are typically young to middle-aged multiparous women who have left lower extremity pain and swelling.^{31,38} Claudication, chronic venous stasis dermatitis, varicose veins, phlebitis, DVT, and pulmonary embolism are also not uncommon presentations for May–Thurner syndrome.^{32,38} Often, patients have a history of prolonged immobilization, recent pregnancy, and/or oral contraceptive (OCP) use.³³ Although exceedingly rare, spontaneous rupture of the iliac vein can occur in patients with May–Thurner syndrome. To date, there have been 35 reports of spontaneous rupture of the iliac vein, with at least 28% occurring in patients with May–Thurner.^{39,40}

Diagnosis

Any patient who presents with left iliofemoral venous thrombosis should prompt suspicion for May–Thurner, particularly female patients with a recent history of immobilization, pregnancy, or OCP use. Although OCP use has long been implicated in the pathogenesis of DVT in young female patients, the possibility of underlying May–Thurner should be considered as patients with May–Thurner benefit from more aggressive therapy than is typically prescribed for DVT alone.³³ We concur with other authors who advocate for the evaluation of May–Thurner in *all* young women who present with left iliofemoral DVT,^{38,41} including those using OCP therapy.

Duplex ultrasonography for the demonstration of iliofemoral thrombus is typically the first study performed in the diagnosis of May–Thurner, although visualization of the iliac veins can be challenging in some patients.^{38,41,42} If May–Thurner is suspected, CTA or MRV both readily demonstrate the compression of the left iliac vein by the right iliac artery (Figure 1). In the presence of thrombus, use of venography by injecting contrast material into the affected extremity may be limited for defining the degree of stenosis of the iliac vein. Once the thrombus has been removed, however, venography can define both the stenosis and the hemodynamic effects of the lesion (Figure 2). A pressure gradient of > 2 mmHg is diagnostic for venous outflow obstruction.^{43,44}

Treatment

The goal of treating May–Thurner in the setting of iliofemoral DVT is to prevent or attenuate symptoms of postthrombotic syndrome, including chronic leg swelling, venous claudication, stasis dermatitis, and ulcers, as well as varicosities associated with valve damage and iliac venous outflow obstruction. Similar to PCD, systemic anticoagulation is the first component of therapy. However, systemic anticoagulation alone is not adequate for the treatment of DVT with May–Thurner, as it fails to address any of the long-term sequelae in this group of patients.^{32,38}

In the acute setting, patients with iliofemoral thrombosis and May–Thurner should be treated aggressively with catheter directed thrombolysis, percutaneous mechanical thrombectomy, and angioplasty and stent placement across the common iliac stenosis. Similar to patients with PCD, an IVC filter should be placed via the transjugular route prior to lower extremity intervention. The patient is then placed prone and access to the popliteal vein is obtained via ultrasound guidance. Although it is possible to pass a catheter across the thrombus and initiate thrombolysis for 24 hours, we agree with Murphy et al³³ that

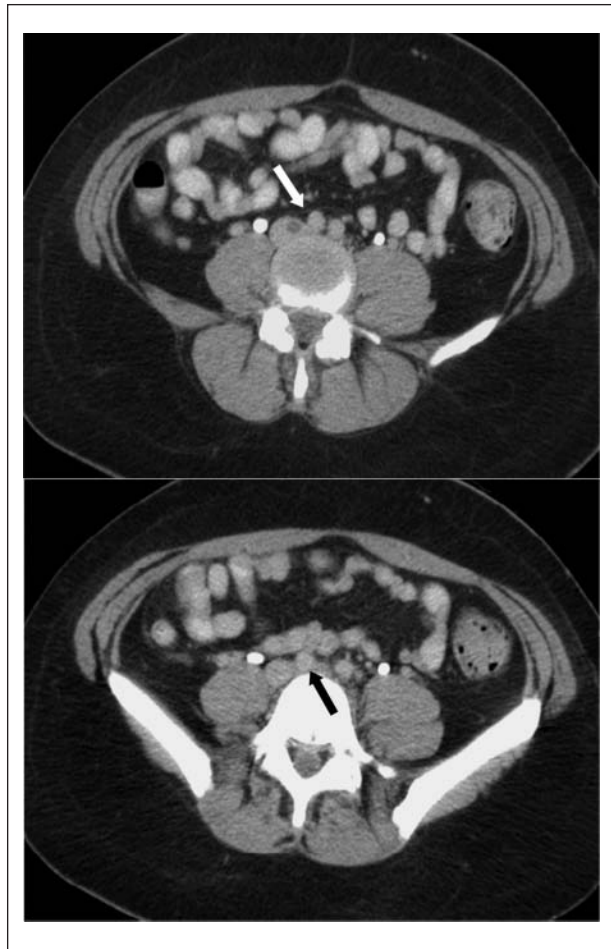


Figure 1. May–Thurner syndrome: Computed tomographic angiography demonstrating compression of the left iliac vein by the right iliac artery.

primary treatment with mechanical thrombectomy either with the Trellis (Covidien/Bacchus Vascular, Santa Clara, CA) thrombectomy device³³ or with pulsed infusion (and subsequent aspiration) of thrombolytic using the AngioJet (Medrad Inc, Warrendale, PA) system followed by angioplasty and stent placement across the distal iliac obstruction is a better strategy for complete thrombolysis. Achieving full resolution of the outflow obstruction enhances flow in the deep venous system. Once the outflow obstruction has been treated, an additional 24 to 48 hours of thrombolysis is typically required.

It should be stressed that stent placement is an essential component to therapy as May–Thurner is an acquired disorder from mechanical obstruction. Placement of a large (12 to 14 mm) self-expanding stent across the stenosis and into the IVC helps prevent stent migration. The success of stent placement is high in acute DVT with



Figure 2. May–Thurner syndrome: Angiographic demonstration of severe stenosis of the common iliac vein.

underlying May–Thurner syndrome, with 2-year patency rates for primary and secondary iliac vein compressions approaching 95% and 100%, respectively.⁴⁵⁻⁴⁷

Although percutaneous intervention is first-line therapy for May–Thurner with DVT, open surgical procedures have been used historically, and today, for those who have failed endovascular intervention. Operative intervention for May–Thurner with acute thrombosis includes thrombectomy with adjunctive arteriovenous fistula and relief of the distal iliac obstruction via dissection of the right common iliac artery off the left common iliac vein.³⁸ Patch angioplasty may be performed if a defect in the left iliac vein is encountered.⁴⁸ Additional surgical interventions for the treatment of venous spurs from underlying May–Thurner include saphenofemoral

crossover, arterial repositioning, peritoneal flap, fascia lata sling, prosthetic bridging, aortic elevation, and ilioiliac crossover bypass.⁴⁹

Nutcracker Syndrome

Nutcracker syndrome (NCS) occurs as a result of left renal vein (LRV) outflow obstruction due to extrinsic compression from surrounding anatomic structures.⁵⁰ NCS is a rare entity typically associated with a thin body habitus. Anterior and posterior forms of NCS have been described. Anterior nutcracker occurs as a result of LRV compression between the superior mesenteric artery (SMA) and the aorta, and it has been hypothesized to be a result of decreased retroperitoneal fat leading to a narrowing between the SMA and the aorta. Posterior nutcracker, in which the LRV is compressed between the aorta and the vertebral column, may be the result of paraspinous muscle wasting and weight loss.⁵⁰⁻⁵² As with May–Thurner syndrome, the exact incidence of anatomic renal vein compression is unknown, although it has been reported that up to 72% of patients undergoing CT demonstrate distended proximal LRV with compression of the outflow by the SMA.⁵³

Clinical Findings

NCS typically afflicts 2 subsets of patients: women in their third to fourth decade who present with pelvic congestion symptoms, and children and adolescents who typically present with self-limiting symptoms.⁵⁰⁻⁵² Although NCS has a variable presentation,⁵² the most common complaints are gross hematuria with abdominal and/or flank pain that is exacerbated by physical activity. One classic presentation of NCS occurs when patients are symptomatic in the recumbent or very erect postures, because these positions decrease the angle between the SMA and the aorta and lead to elevation of left renal vein pressure.^{50,54}

Diagnosis

History and physical exam are important for the diagnosis of NCS. However, given the frequency of LRV compression on imaging, a thorough workup of other causes of hematuria and abdominal pain is critical to the diagnosis of NCS. Younger adolescent patients can have an associated chronic fatigue-type syndrome whereas women in their 30s and 40s can have disabling pelvic congestion. NCS is associated in young patients with a lower body mass index. Nearly 10% of male patients will have a varicocele⁵⁰ on physical examination whereas women can present with vulvar, gluteal, and lower extremity



Figure 3. Nutcracker syndrome: Computed tomographic angiography demonstrating compression of the left renal vein.

varices.⁵² A complete blood count and urinalysis can detect significant blood loss as well as hematuria and proteinuria.⁵⁰

There is no clear consensus for appropriate imaging in the diagnosis of NCS. As previously stated, asymptomatic LRV compression is not an uncommon finding suggesting that the nutcracker appearance of the LRV is a normal variant in anatomy.^{50,53} DUS can be used in the diagnosis of NCS to evaluate for LRV stenosis as well as demonstrate collateral vein distention.^{51,54,55} However, DUS is less useful in predicting the presence of a pressure gradient across the left renal vein.⁵⁶

CTA and magnetic resonance angiography have also been used in the diagnosis of NSC by demonstrating the LRV anatomy as well as determining extent of associated gonadal and pelvic venous distention and eliminating other causes of hematuria⁵⁰⁻⁵² (Figure 3). Venography coupled with demonstration of the reno-caval pressure gradient of greater than 3 mm Hg are considered the gold standard in the diagnosis of NSC but are typically only performed when the diagnosis is uncertain.^{51,52}

Treatment

Patients younger than 18 years and patients with microscopic or intermittent hematuria may be closely followed as spontaneous resolution is known to occur.^{51,57} In patients with severe and persistent symptoms, surgical intervention

should be considered.^{48,49} Surgical intervention includes LRV or SMA transposition, LRV or gonadocaval bypass, nephropexy with excision of renal varicosities, nephrectomy, renal autotransplant, and intra- and extravascular stenting.^{50,51}

The most commonly reported treatment of NCS is LRV transposition into the infrarenal IVC.⁵⁸ Reed et al⁵⁶ have reported 11 patients who underwent left renal vein transposition for NCS with mean follow-up of 39 months. The authors found that symptoms of hematuria resolved in all of their patients and flank pain resolved or improved in 8 of 10 patients.⁵⁶ This is similar to outcomes of open surgical interventions reported by other groups.⁴⁶ Hartung et al⁴⁶ have recently reported the first laparoscopic transposition of the LRV for NCS with no residual stenosis and resolution of hematuria after 12 months.

Endovascular therapy has recently been attempted for the treatment of NCS and has demonstrated less than optimal results. Angioplasty without stent placement of the LRV has limited effectiveness for the long term relief of venous hypertension. While stent placement in this position is technically feasible, long-term results are disappointing in that the pulsatility of the SMA-aortic narrowing over the stent has led to stent migration and embolization^{46,52} as well as thrombosis.⁵⁹ Using a wide and long stent may prevent stent embolization into the right atrium, but migration into the IVC has been noted in the small series of reports.

A thorough review of NCS was presented in *Perspectives in Vascular Surgery and Endovascular Therapy* in June 2009 and is an excellent reference for additional information.⁵²

Conclusion

Although rare, stenosis and thrombosis of the deep veins can lead to significant pathology that presents a vexing clinical problem for both the vascular surgeon and patient. Although endovascular therapy has evolved as the primary intervention for phlegmasia cerulea dolens and May–Thurner syndrome, it should not be forgotten that fasciotomy of the affected extremity is an important adjunct for prevention of ischemic necrosis and venous gangrene in the setting of phlegmasia cerulea dolens. Although percutaneous management for common iliac vein stenosis is highly successful, angioplasty and stent placement for left renal vein stenosis has only limited success at this time.

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