Diagnosis and Treatment of May-Thurner Syndrome

Manu Rajachandran, MD, FSVM; Robert M. Schainfeld, DO
From Memorial Hospital, York, Pennsylvania, and Massachusetts General Hospital, Boston, Massachusetts.

ABSTRACT: In 1908, McMurrich described the presence of strictures in the common iliac vein that were believed to be responsible for the increased incidence of left leg deep-vein thrombosis (DVT). This syndrome would eventually become known as iliac vein compression syndrome or May-Thurner, Cockett’s syndrome, or nonocclusive iliac vein lesion. Left iliac vein compression from the contralateral right common iliac artery, against the posterior fifth lumbar vertebral body, is estimated to comprise 49% to 62% of cases of left lower extremity disease. Although there is some degree of iliac vein compression present as a normal anatomic variant in otherwise healthy patients (>50% compression) in up to 25% of patients, those who experience DVT frequently have anatomically abnormal veins with spur formation and are at high risk of developing recurrent DVT and post-thrombotic syndrome. Herein we describe the presentation, diagnosis, and management techniques for May-Thurner syndrome.

VASCULAR DISEASE MANAGEMENT 2014;11(11):E265-E273

Key words: deep vein thrombosis, anticoagulation, thrombolytic therapy, thrombectomy, endovascular therapy

The peculiar predilection for deep-vein thrombosis (DVT) to involve the left lower extremity in humans has been long recognized in clinical medicine. Virchow was the first in 1851 to observe that iliofemoral DVT was 5 times more likely to occur in the left leg as compared to the right leg. In 1908, McMurrich described the presence of strictures in the common iliac vein, that were believed to be responsible for the increased incidence of left-leg DVT. May and Thurner’s discovery in 1957 of vascular thickening in the left common iliac vein where it was crossed and compressed by the right common iliac artery, more than 100 years after Virchow’s findings, definitively linked the vascular anomaly of focal segmental venous fibrosis or “venous spur,” to the genesis of iliofemoral DVT. Their findings would eventually be the germ of a clinical entity that would become known by a multitude of names such as iliac vein compression syndrome, May-Thurner syndrome (MTS), Cockett’s syndrome or nonocclusive iliac vein lesion. Left iliac vein compression from the contralateral right common iliac artery, against the pos-
The true clinical prevalence of MTS is unknown, but it has been postulated to range in incidence from 18% to 49%, in patients with left leg DVT. The syndrome most commonly presents as an acute DVT. The clinical incidence of DVT related to MTS, however, is quite low, in the range of 2% to 3%. Patients can also present with left lower extremity pain and swelling, or with chronic venous insufficiency without thrombosis.

Possible mechanisms for the syndrome on the macrovascular level include vascular trauma to the vein from repetitive compression from the overlying pulsating artery, causing elastin and collagen deposition in the iliac vein, which eventually leads to spur formation. May and Thurner, in their initial study of 430 cadavers, found obstructive lesions in 22% of left common iliac veins and observed 3 different histologic types of spurs, including a lateral spur, a central spur, and a web of multiple fenestrations, which they termed partial obliteration.²

**CLINICAL PRESENTATION**

Clinical features of MTS include a female predominance, with two common variants in presentation. The classic acute presentation is a woman between 20 and 40 years of age presenting with a DVT either associated with a plausible explanation or identifiable risk factor (i.e., provoked), or unprovoked, without a discernible etiology. Without definitive treatment, chronic limb swelling, recurrent DVT, and venous claudication may develop. The less common chronic presentation involves progressive pain, unilateral left leg swelling, varicose veins and venous ulcers without antecedent acute thrombosis. Many patients with May-Thurner anatomy remain entirely asymptomatic throughout their adult life. Rare cases of right common iliac vein compression have also been described, usually in patients with left-sided inferior vena cava.⁵ ⁶ A thorough history and physical exam is mandatory in young patients presenting with unilateral lower-extremity edema. A concurrent evaluation for thrombophilia is required in these cases, because up to 67% of patients with iliofemoral DVT or MTS can manifest some variant of thrombophilia.⁷
In patients presenting with signs or symptoms of MTS, the diagnosis may be made by a variety of methods. Duplex ultrasonography has long been the initial screening exam for lower-extremity DVT due in part to its portability and ease of use. Lensing et al in 1989 observed a sensitivity and specificity of 91% and 99% respectively for the detection of proximal DVT with B-mode ultrasound, using the single criterion of vein compressibility. Noninvasive testing may be employed in supporting the diagnosis of iliofemoral DVT, with findings on duplex ultrasonography consisting of narrowing of the iliac vein at the level of the artery, abnormal Doppler flow below the level of compression and absent variation of flow within the common femoral vein when patient inhales and exhales.

The gold standard for diagnosis of MTS historically has been contrast venography. This invasive study can delineate the location and extent of thrombosis, help differentiate between acuity and chronicity of the occlusion, and aid in the detection of truncal venous malformations of the femoral vein, such as duplication of the femoral vein, which can occur in up to 12% of patients and is usually bilateral in distribution. Venography has also helped identify up to 3 common angiographic patterns in MTS. These include focal stenosis or collateralized short-segment occlusion of the left common iliac vein, acute iliofemoral venous thrombosis with the underlying lesion being revealed after successful thrombolysis, and chronic isolated thrombosis of the left common and external iliac veins with collaterals arising from the common femoral vein.

Venography entails inserting a catheter directly into the adjacent veins, and administering a contrast agent or dye into the vein, which may show compression of the iliac vein with spur or web formation. CT venography and magnetic resonance (MR) venography are two newer, minimally invasive modalities that may be used to evaluate the iliac veins. The advantage of both of these technologies is that they may detect occult pelvic masses and other causes for extrinsic venous compression as well as provide important information about venous architecture and extent of thrombus.

The sensitivity and specificity of MR venography approached that of invasive venography for the detection of iliofemoral thrombosis, in one prospective study. In cases where a therapeutic intervention appears indicated, intravascular ultrasonography (IVUS) has been extensively relied on for the diagnosis and documentation of iliac vein stenosis and dynamic compression and to facilitate in planning of stent procedure.

TREATMENT

May–Thurner syndrome should be treated only when it is symptomatic. The treatment of MTS in the setting of iliofemoral DVT is aimed at preventing the sequelae of veno-occlusive disease including PTS, venous claudication, venous stasis ulceration, and chronic venous insufficiency arising from damage to venous valve architecture. Anticoagulant therapy, such as intravenous heparin or low molecular weight heparin, which are administered subcutaneously, with an eventual transition to warfarin or coumadin, is the mainstay of treatment for patients with acute DVT. This pharmacologic regimen prevents thrombus propagation and cephalad extension into the pulmonary artery but does little to dissolve any existing chronic clot. It is therefore inadequate to treat the long-term sequelae of iliofemoral DVT associated with MTS, as mentioned previously. Definitive therapy

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of symptomatic MTS usually requires revascularization to relieve venous hypertension. Endovascular recanalization can be achieved by a multitude of modalities. Acute MTS is most effectively treated with catheter-directed thrombolysis (CDT), mechanical thrombectomy (MT), and adjunctive percutaneous balloon venoplasty and stenting. This is usually best accomplished by antegrade percutaneous access with ultrasound guidance of the ipsilateral popliteal vein, with the patient in the prone position. This approach allows treatment of the occluded venous segment in the direction of flow, and minimizes catheter-related damage to the venous valves, as opposed to a contralateral retrograde approach or ipsilateral antegrade common femoral vein puncture. Because less than 1% of iliofemoral venous thrombosis is solely confined to the iliac venous segment, the more distal popliteal vein access route enhances the ability to access and lyse thrombus in the common femoral venous segment, thus improving overall technical success rates. Other venous access points have included the small saphenous vein, with catheter insertion into the popliteal vein past the sapheno-popliteal junction, and in certain instances, the posterior tibial vein. Traditional therapy involved catheter-directed thrombolysis often up to 48 hours or longer, followed by balloon angioplasty of the underlying outflow lesion, usually found at the level of the confluence of the common iliac vein with the inferior vena cava (IVC).

Recently developed treatment paradigms have sought to shorten the recanalization process by acceleration of thrombolysis of the venous occlusion. The added benefit of this method is the reduction in bleeding risk, due to a lower dose of infused lytic agent, along with the shorter duration of exposure to lytic therapy. Endovascular therapy with CDT and/or percutaneous MT refers to a heterogeneous group of devices used to fragment, ablate, or extract intravascular thrombus in an effort to produce more rapid and efficacious lysis. PMT has a number of advantages over CDT alone, including more rapid restoration of flow in situations where limb viability is compromised. This therapy is most likely to be successful when thrombus is acute (<14 days old) and much less effective when the clot is chronic (>4 weeks old). Lytic drugs include alteplase, tenecteplase, reteplase, streptokinase, and urokinase. None, however, have specific FDA approval for use in DVT.

Vedantham et al, using a variety of thrombolytic agents and MT devices, employed CDT with adjunctive thrombectomy to treat 28 symptomatic limbs in 22 patients with MTS. They achieved procedural success in 82% of limbs treated, with a major bleeding rate of 14%. Mean infusion time was approximately 17 hours, and mean per-limb total dosages of lytic agent were lower than in previously reported studies of DVT thrombolysis. Serial venographic analysis in this study revealed inefficient thrombus removal using MT alone and far more substantial thrombus removal when using both CDT and MT. Typical thrombolytic protocols now incorporate both CDT and MT in synergistic fashion to facilitate venous recanalization.

A number of mechanical thrombectomy catheters with different mechanisms of action are commercially available. These include the Trellis device (Covidien), which uses a sinusoidal nitinol wire to mechanically disintegrate thrombus while lytic agent is infused between proximal and distal occlusion balloons, and the AngioJet rheolytic thrombectomy catheter (Boston Scientific), which can be used in the pulse spray mode to
deliver lytic agent directly into the clot, and then in the aspiration mode to remove thrombus. Other devices that have historically been used for thrombus removal are the Oasis device (Boston Scientific), the Trerotola percutaneous thrombectomy device (Teleflex), and the Amplatz thrombectomy device (Microvena). Recent experience with the EKOS Endowave system, which uses ultrasound-accelerated catheter-directed thrombolysis to treat iliofemoral DVT, has also been favorable.19 This device uses ultrasound to thin and expand the fibrin component of the thrombus, thus exposing plasminogen receptor sites to increase the efficacy of the thrombolytic agent; the device does not mechanically remove clot. A pilot study of the device in 12 patients with iliofemoral DVT, using either rtPA and urokinase as lytic agents, resulted in a technical success rate of 85% (complete clot lysis), with minimal major bleeding, and no instances of pulmonary embolism. Routine IVC filter placement was not performed in this study.20

Once the occluded iliac vein is rendered patent by the modalities described above, in cases of suspected iliac vein compression, contrast venography with adjunctive IVUS are complementary tools to confirm the diagnosis and guide therapy (Figure 2). It is “de rigeur” to perform balloon venoplasty of the underlying outflow obstruction followed by stenting of the segment in order to ensure long-term success. These measures not only prevent early venous reocclusion but also improve primary patency rates to 70% to 80% in the first year following treatment. The degree of lysis also has been found to be a major predictor of early and long-term patency. More complete clearance of thrombus yields venous patency rates in excess of 75% in most studies, whereas incomplete lysis (>50% remaining residual clot) leads to poor (<40%) patency.15 Stenting relieves the mechanical obstruction in the common iliac vein, offers definitive immediate technical success, and improves long-term vessel patency. A large self-expanding

Figure 2. Iliocaval venogram after percutaneous mechanical thrombectomy (A). Venoplasty of occluded left common iliac vein (CIV) presumed due to iliac vein compression (May-Thurner). Note inferior vena cava (IVC) filter deployed after retinal hemorrhage during tPA (B). Wallstent (Boston Scientific) deployed in IVC/CIV confluence restoring patent iliac vein (C).
A stent (12 mm to 16 mm in diameter) is deployed across the stenosis and extended into the IVC. It is generally oversized slightly to the diameter of the common iliac vein, and is allowed to “mushroom” up into the IVC, just above the iliocaval junction, so that anchoring is secure and the risk of stent migration reduced. Intravascular ultrasound can also be helpful in these instances, to size the stent appropriately to the dimensions of the vessel and to select the optimal length of stent that will allow secure anchoring at the iliocaval junction. Intravascular ultrasound can also delineate the adequacy of a balloon percutaneous transluminal angioplasty result, quantify the presence of residual thrombus within the treated segment of vein with greater clarity than venography, and help assess the need for further thrombus removal. Once the outflow obstruction is treated, thrombolysis may be continued for an additional 24 to 48 hours for optimal clot resolution. In some studies of acute DVT with underlying MTS, primary 2-year stent patency rates for primary and secondary iliac vein compression approach 95% to 100%.21,22

Percutaneous MT with CDT and venous stenting provides optimal benefit in young and functionally intact patients who have acute (<14 day) presentation of extensive proximal (IVC or iliofemoral vein) thrombus, or in patients with phlegmasia cerulea dolens. The optimal window for lysis is somewhat controversial, but existing data suggest that lytic therapy should be initiated within 10 days to 21 days of acute symptom onset. Older clot has significant heterogeneity of composition, with chronic thrombus interspersed with acute or subacute thrombus, and would likely be more resistant to thrombolytic therapy. Venous stenting has been used to successfully treat iliac vein obstruction, of various causes, including post-thrombotic occlusion, iliac vein compression, and obstruction from malignancies. Patients with chronic iliac vein obstruction from extrinsic compression fare better when treated with stenting as compared to those patients who have occlusive venous disease (Figure 3).

Figure 3. Venogram of severely stenotic iliac vein in 40-year-old female with significant edema and varicose veins of left thigh and calf. Retrograde filling of internal iliac vein with pelvic collaterals and ascending lumbar vein is seen (A). Percutaneous transluminal angioplasty (PTA) of iliac vein (B). Post-PTA venography with significant residual stenosis due to elastic recoil (C). Venogram following successful revascularization of iliac vein with Wallstent (Boston Scientific) (D).
This is reflected in the 6-year follow-up results for iliofemoral venous stenting, with cumulative patency rates of 79% to 100% for nonthrombotic vessels, as compared to 57% to 86% in individuals with thrombotic occlusive disease. Complementing these excellent technical and patency rates, recently published series report laudable clinical outcomes with reduced pain, swelling and improved quality of life in those patients who underwent venous stenting.

For those patients with chronic iliofemoral venous occlusion, thrombolytic therapy can be omitted in favor of direct recanalization with balloon venoplasty and stenting. In those cases that remain recalcitrant to MT and CDT, surgical intervention should be considered. This usually involves operative venous thrombectomy and creation of a temporary arteriovenous fistula to prevent recurrent thrombosis, usually between the saphenous vein and superficial femoral artery, and this was historically the only intervention available for treatment of patients with iliofemoral obstruction prior to the introduction of balloon venoplasty. Compared to anticoagulation alone, operative intervention is associated with reduced leg swelling and ulceration with sustained long-term patency rates of 65% to 85% in the long term. Owing to reduced procedural morbidity or complications, endovascular approaches are recommended as first-line treatment in most patients, but in those individuals deemed at high-risk for bleeding with thrombolytic therapy, surgery may be considered where appropriate expertise and resources are available.

**COMPLICATIONS**

Complications have been reported after stent implantation, which include bleeding at site of venous access, and more serious complications such as intra-abdominal and retroperitoneal bleeding. A recent review of 16 retrospective case series of CDT with MT for DVT reported transfusion rates ranging between 4.2% and 14% in 130 patients. The most potentially devastating bleeding complication is intracranial hemorrhage, which is quite rare at 0.2%, and pulmonary embolism in 1%. These complications are more often observed with the use of adjunctive thrombolytic therapy. Stent thrombosis is a rare complication, and was observed more frequently in thrombosed (10%) vs nonoccluded veins (1%).

**FOLLOW-UP**

Patients are usually placed on a short-term regimen of enteric-coated aspirin (81 mg to 325 mg) and clopidogrel (75 mg daily) for at least 4 weeks to 6 weeks post intervention to prevent stent thrombosis. Anticoagulation with warfarin is initiated in patients who present with acute DVT and MTS and is continued for a specified duration based on established clinical criteria (3 months to 6 months). Aspirin or clopidogrel may be continued as the sole antiplatelet agent indefinitely after the 4-week to 6-week time period for dual antiplatelet therapy has elapsed. In patients with documented thrombophilia, long-term anticoagulation with warfarin may be considered. Patients are followed clinically and with periodic duplex venous ultrasound exams of the iliofemoral venous stented segment to assess for long-term patency. Repeat venography and IVUS study are reserved for those patients with persistent, recurrent, or new signs and symptoms suggesting venous occlusion or thrombosis.
CONCLUSION

Iliac vein compression is a source of significant risk and morbidity and appears to be relatively underdiagnosed. It should be considered as a possible cause of unexplained left-leg DVT or when persistent swelling and pain exist in the left limb. Venous balloon angioplasty and stenting appears to be a safe, simple, and efficient method to treat iliofemoral vein obstruction or narrowing from compression. Because patients with chronic venous disease are young and have excellent life expectancy and a favorable prognosis, venous stenting must be offered to maintain clinical improvement and high rates of patency in the long term. The chronic effects of stents in the venous system remain largely unknown, and as such several more years of monitoring the efficacy and safety of this therapy is required in all patients with veno-occlusive disease due to May-Thurner syndrome.

Editor's note: Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no financial relationships or conflicts of interest regarding the content herein.

Manuscript submitted July 15, 2013; provisional acceptance given October 3, 2013; final version accepted May 12, 2014.

Address for correspondence: Manu Rajachandran MD, FSVM, Memorial Hospital, 325 South Belmont Street, York, PA 17405. Email: stentdoc63@yahoo.com.

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