Review Article

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May Thurner syndrome: Sixty years later

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Abstract

May-Thurner syndrome (MTS) was described sixty years ago. Once ignored for several years, it is currently a recognized pathology in the vascular surgery community; but not long ago due to several factors, it was underdiagnosed and sub-optimally treated. In the last 20 years, with renewed interest in venous pathology, technical imaging advances and the recent interventional procedures, it has become a better known disease. On the other hand, nowadays the easiness in diagnosis and treatment of the syndrome has lead to overtreatment of such patients. In this article, we do a historical review and describe the significant advances and current management of May-Thurner syndrome.

Keywords

May-Thurner syndrome, iliac vein thrombosis

Introduction

Since the original publication by May and Thurner in the Angiology Journal at 1957 with the paper "The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins", significant advances in its understanding have occurred. Nowadays MTS is an entity much better known, well established by the new imaging development and interventional treatment methods. But, this has not always been so, In the first years after its description MTS was considered a rare disease and commonly under-diagnosed.

The late 50's, XX century

Previous to the original article of May and Thurner in 1957. There were some ancillary reports about the iliofemoral segment deep vein thrombosis (DVT), of them, the first report belongs to Virchow in 1851; He described the left leg deep venous thrombosis predominance over the right one.[1]

Half a Century later, Mc Murrich studied 107 cadavers with the same pattern of DVT, finding higher prevalence in the left leg 29.9% than in the right 2.8%, this study included both neonates and adults suggesting a possible congenital origin.[2]

Ehrich in 1943 report of 412 autopsies with special attention to the iliac veins dissection, and suggested an acquired etiology for the left iliac vein obstruction.[3]

May and Thurner knew about the previous study and in an effort to disclose a cause for the DVT they dissected 420 cadavers, their findings indicated an important focal intimal venous thickening and septa formation in 22% of the subjects, naming them "spurs". They hypothesized that: "The repetitive trauma caused by the right common iliac artery (RCIA) pulsation over the left common iliac vein (LCIV) produces endothelial injury, collagen and elastin accumulating in the vein intimal layer originating webs and spurs" (central, lateral and fenestrated) (Figure 1). This important research was published in Angiology, the premier journal in vascular medicine at that time.[4,5]

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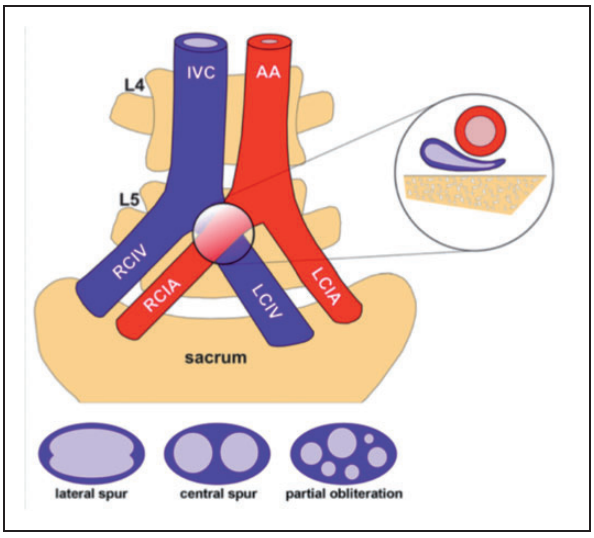

Figure 1. Anatomy of May-Thurner Syndrome and types of spurs.
RCIA: right common iliac artery; RCIV: right common iliac vein; LCIA: left common iliac artery; LCIV: left common iliac vein; IVC: inferior vena cava; AA: abdominal aorta; L4 and L5: fourth and fifth lumbar vertebrae.

The 60's and 70's, XX century

Cockett et al correlated the DVT incidence, post-thrombotic syndrome (PTS) and iliac vein compression clinically and pathologically and they called it "Iliac vein compression syndrome"[6,7] After those reports some authors used the Term "May-Thurner-Cockett syndrome" or "Iliac vein compression syndrome" to describe this entity. However, on the late 60's and all the 70's there were only sporadic case reports, probably related with diagnosis difficulties.[8]

The 80's and 90's, XX century

In the early 80's a worldwide renewal interest for venous pathology related to imaging development and interventional techniques, including new generation of CT scans, MRI, catheter technology, and a multidisciplinary involvement in the diagnosis and management of venous pathology revitalized the specialty.[9]

The late 80's saw thrombolysis emergence on DVT; few years later, pharmaco-mechanical and advanced imaging methods increased the MTS diagnosis and management .

In the 90's, the direct thrombolysis with catheter (CDT) for DVT in the Iliofemoral region was widely implemented,[10,11] and modern venous system imaging disclosed, that about 50% of these patients had iliac vein stenosis, confirming that many patients with DVT had MTS.[12]

Binkert et al in 1998, reported successful use of left iliac vein angioplasty/stenting with 100% patency at 3 years follow up. Later on, worldwide medical centers corroborated the endovascular techniques efficacy in patients with MTS.[13]

Compression and endoluminal defects

Since the original article of May and Thurner the association of intraluminal spurs due to the pulsation of the rigth iliac artery over the Left common iliac vein (LCIV) causing repetitive trauma and inflammation of the intimal layer in the vein was stated as the etiology of the syndrome. This paradigm was accepted so far. However, Mc Murrich JP. In 1908 Described "The occurrence of congenital adhesions in the common iliac veins and their relations to thrombosis of the femoral and iliac veins."[2] But, this notion was disregarded until recently. In the early 2000's some authors emphasized the difference between MT Anatomy and MT Syndrome.[14,15] Others authors reviewed the embryological development of the ilio-caval segment in humans and compared it with the chimpanzee's and concluded that, despite the similarities in anatomy; the absence of MTS in chimpanzees is due to different gravitational forces.[16] These differences suggested that LCIV is necessary but not sufficient to cause MTS; when symptoms occur a whole array of data occur ranging from acute pain and swelling in the leg to venous claudication, and chronic presentation as venous insufficiency and/or pelvic congestion syndrome in women.[17–28] Recently Lee BB, et al. In a consensus document of the International Union of phlebology (2015) the Hamburg classification of congenital venous malformations was updated and the spurs seen in MTS correlated with truncular venous malformations occurring between the 3rd-5 th months of intrauterine life.[29] Similar intraluminal spurs were described in the jugulars and in the primary Budd Chiari syndrome. In the jugular veins Zamboni et al studied the ultrastructure of intraluminal defects by scanning electron microscopy in patients with chronic cerebrovascular insufficiency; they found lack of endothelial cells in the internal jugular vein intraluminal obstacles. However, it was not clear this finding is primary or caused by altered hemodynamic forces or past posthrombotic remodeling.[30]

Also in the Budd-Chiari syndrome (hepatic venous outflow tract obstruction) . The thrombosis is a result of various factors; presentation and etiology may differ between Western and Eastern countries. Myeloproliferative disease is present in 40% of patients, the other 60% is caused by congenital endoluminal alterations: a) segmental stenosis, b) segmental occlusion, c) membranous stenosis, d) membranous

occlusion or cord-like occlusion as showing by magnetic resonance venography.[31–33]

These recent studies suggests that MTS has a congenital substratum, but the Arterial pulsations over the iliocaval segment it is an important factor causing the endothelial vein lesions to evolve whether or no to originate symptoms.[34,35]

Current diagnostic techniques

Diagnosis of MTS requires demonstration of the venous stenotic lesion in an appropriate anatomic location.[36] In patients with proximal DVT, history of DVT or venous insufficiency with lower extremity swelling the initial study is duplex ultrasound; in the absence of thrombus CT venography and/or MR venography are indicated.

Color venous duplex ultrasound (CVDU)

After clinical suspicion of DVT, the initial noninvasive diagnostic test is CVDU, its sensitivity is 91 percent and specificity 99 percent using compression in proximal DVT. While, CVDU first aim is to rule out DVT, it also evaluates venous reflux time. Venous duplex ultrasound findings of iliocaval DVT are: absence of flow variation, narrowed iliac veins and poststenotic turbulence (noisy signal).[37–39] To evaluate the common femoral vein a linear 4 to 7 Mhz array transducer with a <60 angle of insonation is used, while a 2 to 3 MHz transducer should be used for iliac and caval vessels. B- mode compares vein diameter reduction at the smallest lumen area against normal vein diameter. Peak vein velocity (PVV) is measured in the pre and post stenotic segment; a PVV gradient >2.0 is significant.[40,41] Despite the aforementioned, the deep location of the proximal iliac vein plus others factors (obesity, overlying gas) interfere with ultrasound for an accurate diagnosis of MTS.[42,43] A recent description of a maneuver in asymptomatic patients showed the presence of illusory MTS – With the patient in supine position is very frequent to find the left iliac vein compression; when released the gravitational overload with the subject in semi-settle 45° position, this relief the compression and flow recovery in the left iliac vein-. Corroborated by plethysmography, either in semi-settle and in supine positions, with and without leg elevation. The real MTS is non-reversible and/or associated to intraluminal defects.This maneuver could become an initial screening and avoid more invasive or expensive diagnostic steps.[44,45]

Figure 2. Contrast computed tomography in MTS. White arrow LCIV compressed. Black arrow RCIA.

Cross-sectional Imaging – CT/MR venography

Both studies have more than 95 percent sensitivity and specificity in MTS, but require particular protocols in order to obtain better Imaging. CT venography (Figure 2) using 3–5 mm. cuts visualize structural details (spurs, webs) , ruled out extrinsic compression, identify location and stenosis degree in non-thrombosed veins, shows DVT and collateral pathways.[46–53] When the contrast opacification is suboptimal with the standard (indirect) method a direct technique could be used with good results.[52,53] As with the ultrasound, the patients can be put in different positions (supine or prone) or to use the valsalva maneuver to identify an illusory MTS.[54,55] CT venography advantages over CDUS or venography include lack of operator dependence, clearer pelvic veins images and shorter exam time. However, the radiation dose avoids its use in pregnancy and the use of contrast medium contraindicates its use in patients with renal failure.[52,53] MR venography provides information similar to CT venography with better characterization of the pathology in pelvic and spinal structures including lumbar vertebral degeneration, bulging or protruding intervertebral disks, osteophytes, or spondylolisthesis;[56] further assessment of hemodynamic significance by demonstrating pelvic collaterals and flow reversal (on time-of-flight pulse sequence) within the ascending lumbar veins; hence, either CT or MR venography are an integral part in the evaluation of patients with MTS.[56–58]

Invasive venous imaging

Catheter venography was the gold standard in diagnosing MTS until recently. It is the first step to endovascular treatment, it measures pressure gradients across the stenotic area – a gradient >2 mm Hg at rest and

>3 mmHg during exercise has hemodynamic significance.[17,18,40,53,59] It determines location and severity of the stenosis; to improve its accuracy multiplanar views – AP and lateral projections – are obtained during injection[19,35,43,53] to avoid "the pancaked vein effect" (externally compressed in the AP plane).[20,21,59] So far, none study has validated a specific diameter threshold for a stenotic lesion in the venous system leading to symptoms; that is due to various factors: compliance of veins, volume status, position of the patient. However, a stenosis more than 50% has been accepted empirically to stent for relieving symptoms.[36,37,40,41,53] Confirmation of a stenotic lesion in MTS is made by pressure measurements, there are various methods, but the more accurate is the pullback method – It measures the pressure in the lower inferior vena cava comparing it with the distal iliac vein, and a gradient pressure is obtained.[43,50,53] Venography helps to define collaterals or the presence of congenital venous anomalies,[17–19,50,53,59] it shows blood flow patterns and the presence of thrombi[16,17,18,19,37,59] (Figure 3(a)). However, venography is invasive, time consuming with an increased bleeding risk and does not contribute to extravascular information,[17–19,37,40,50,53] finally patients are exposed to radiation and contrast dye.[18,19,59,60]

Intravascular ultrasound (IVUS)

Nowadays, the gold standard for MTS is venography plus Intravascular ultrasound . IVUS is more sensitive than venography (>98%).[17–19,36,53,61] It provides high-resolution images through high-frequency sound waves from the ultrasound transducer on the catheter.[36,37,41,43,50,62] IVUS shows precisely the morphology of the spur and estimates the severity and distribution of pathology.[63] Two types of IVUS are available, mechanical and solid state (digital and rotational catheters). IVUS catheters use a 0,035 inch wire and are chosen by their maximal imaging diameter and transducer frequency e, g Volcano 60 mm 12Mhz.[18,19,21,35,50,53,63] IVUS provides data on minimal luminal area at compression site, reference lumen area and signs of fibrosis within the vein. Since the inception of IVUS in the turn of this century; It has been considered an integral part of stent deployment. It has advantages in subtle iliac vein pathology, it is useful before intervention – proper vessel sizing – and, after therapeutic interventional procedures; It measures cross-sectional area gain, stent placement, its expansion and In-stent restenosis (Figure 4(a) and (b)). IVUS visualizes wall thickening caused by compression and adjacent structures, e.g. iliac artery; Finally, IVUS identifies subtle stenosis when the vein wall and lumen appears otherwise normal.[17–19,35–37,53,64] IVUS does not utilize contrast or ionizing radiation.[19–21,36,37,53,59] The limitations of IVUS are invasiveness of the procedure, limited extravascular information and in some places lack of availability.[18–21,35,36,43,50,59,65] Overall, IVUS is the single most important advancement occurred in venous pathology so far.

Current diagnostic assessment

In the last two decades the diagnosis and treatment of MTS has evolved more than in the previous 40 years. There have been many published clinical cases and reviews about MTS due to the availability of advanced imaging and endovascular treatment techniques.[18,19,37] In the first decade of this century, the most important advance in MTS was the use of intravascular ultrasound.[15,18,19,53,65]

The real incidence and prevalence of MTS is still unknown. It is estimated to occur in 2-5% of patients with venous disease, some authors indicate it occurs in as many as 22–24% of those patients[16–19,53,59]; Anyway, it is still infrequently diagnosed and undertreated. MTS is more common in young healthy women between ages 20–50 years-old. Recent data shows that MTS is the most significant factor for left sided DVT, being 3-8 times more common than right

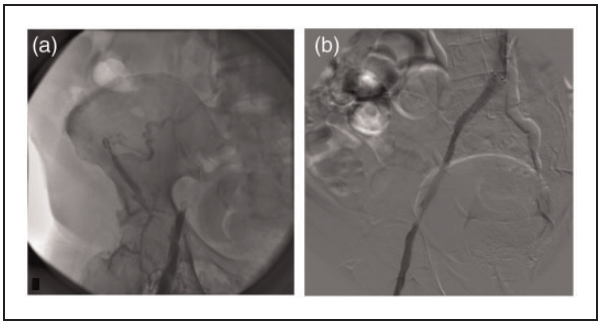

Figure 3. Catheter venography in MTS. a) DVT with collateral circulation. b) left common iliac vein stented.

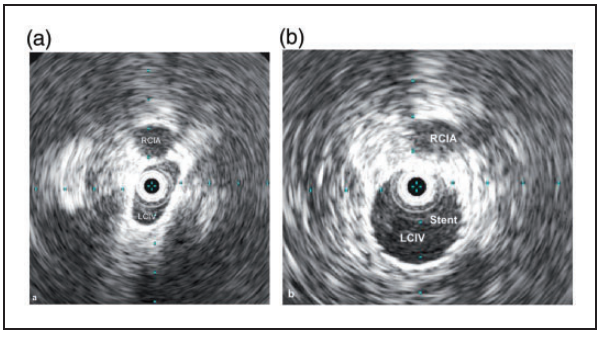

Figure 4. Intravascular Ultrasound (IVUS). a) Stenotic LCIV compressed by RCIA. b) LCIV stent in situ.

sided DVT.[15,18,19] But other variants exist e.g right-sided MTS and compression of the inferior vena cava (IVC) by the right common iliac artery[66–68]; moreover, rare MTS are described: e.g. rupture of the iliac vein, secondary to an iliac artery stent, prostate hypertrophy, in patients with foramen ovale and cryptogenic stroke and pelvic congestion syndrome.[69–77]

Recently OU-Yang L evaluated 79 patients with MTS by CT scans and classified them in two groups: 1) standard MTS in younger and, 2) degenerative MTS in older patients.[15]

Previous studies showed that left common iliac vein compression is necessary but not sufficient to cause MTS. While the compression by the right common iliac artery may cause an indentation and grove on the left common iliac vein; it is the relative positioning of the right common iliac artery with respect to the fifth lumbar vertebrae that is probably the etiology for MTS development.[16–19,59,78] So, the essential difference between MT Anatomy and MTS is the presence of intraluminal spurs that compromised venous outflow and the development of collateral vessels.[79] Although, some authors disagree with the term "MT Anatomy" and call it "anatomical variation"[80]; In practice it is widely used and accepted to make the concept clear. In a recent UIP consensus conference the fact that the intraluminal defects in the venous system are congenital truncular malformations between the third and fifth months of intrauterine life and no generated by the compression of the right iliac artery was stated.[29] We think that the conversion of MT anatomy in MTS is multifactorial and more research is needed to define the precise pathophysiological mechanism.[16,18,19,79]

Current treatment of MTS

It depends upon the presence of symptoms, severity and whether or not DVT is present.

1) In patients with non-thrombotic MTS symptomless or with mild symptoms.

(CEAP 1–3) conservative treatment with compression stockings is enough.[18,19,79]

2) In patients with non-thrombotic MTS with moderate to severe symptoms (CEAP 4–6) Angioplasty and stenting is indicated[37,64,79]

3) Thrombotic MTS without contraindication to lytic therapy; Initially anticoagulation, then catheter directed thrombolysis and/or pharmaco-mechanical thrombolysis. Finally angioplasty and stenting; after this, the rate of post-thrombotic syndrome is less than 10%, without treatment it is 80 to 90%.[37,64,65,79]

4) In patients with thrombotic MTS with contraindications to lytic therapy, mechanical (suction) thrombectomy or open surgical thrombectomy are indicated; Then angioplasty and stenting.[18,19,37,64,65,79]

The endovascular approach begins with: 1). A presumptive MTS based on clinical suspicion. 2). CDVU with the Zamboni maneuver to avoid an illusory image[80]; Then, either CT Venography or MR venography. 3) Venography and IVUS to demonstrate and confirm the degree of left common iliac vein stenosis and pelvic venous collaterals. 4). Then, angioplasty of the affected vein stenosis segment and finally. 5) Stenting; Stents in MTS must have high radial force, e.g. Wallstent, or better now Vici (Boston Scientific) and Venovo (Bard) to resist the shears forces left common iliac vein is subjected to under for life (Figure 3(b)).[18,19,44,65,79,81]

The wallstent (Boston scientific) is the stent most used off label in the US; It improved the patency and symptoms when compared to just angioplasty. However, it has a high rate of recoil and significant foreshortening (83.75%) when deployed making it difficult to position accurately at the compression site; for this, the proximal landing zone must be 3–5 cm in the IVC.[82–86] Nitinol stents were developed to overcome the Wallstent problems; Nitinol stents do not foreshorten as much as the wallstent e.g Cook vena 14.20%, Vici 20% of the initial length; the implanted length should be near-nominal of the intended when size properly, so the foreshortening is not significant providing a more accurate positioning of the stent[85–88]; hence, they are not put in the IVC. Several of these stents have good outward and compression radial force and crush resistance. There are no comparative data between the Wallstent and the new nitinol stents with relation to patency and target lesion revascularization; the stent must be large enough to bypass the stenotic area and the distal landing zone has to be wide enough to avoid blood flow perturbations.[82–89] There are various nitinol venous stents developed and approved in Asia and Europe since 2010 (Vici Boston, Scientific, Zilver Vena Cook, Sinus Venous Optimed, Venovo Bard, Abre Medtronic). But, until now, just two of them are FDA approved – Venovo (Bard) in March 2019 and Vici (Boston Scientific) – in May 2019.

Clinical experience with the Wallstent in the iliofemoral venous region in the last two decades showed its efficacy as reported in one of the largest retrospective study in 982 lesions, the five year primary patency, assisted-primary patency and secondary cumulative patency rates were 79%, 100% and 100% in non-thrombotic disease and 57%, 80% and 86% in thrombotic disease, respectively.[84,86] A recent prospective, multicenter, multinational, single arm study with the Venovo stent (VERNACULAR trial) in 156 patients, 219 stents were successfully deployed. The primary patency at 12 months was 88.3% significantly better than reported (74%) from the venous stent literature ($p < 0.0001$). 84 patients had PTS and 72 had non-

thrombotic iliac vein stenosis.[86,90] In the VIRTUS trial with the Vici Stent (Boston Scientific) 170 patients (127 post-thrombotic and 43 non-thrombotic) were studied. Primary patency based on both venography and CDUS when venography data was not available was 84%. Primary patency based on venography only (available in 125 patients) was 79.8% for post-thrombotic lesions and 96.2% for non-thrombotic lesions. There were 98.8% freedom from mayor adverse events.[86,91] Still, there is no comparative data between venous stents following angioplasty and stenting for MTS.[86] In PTS patients oral anticoagulation for at least 6 to 12 months or indefinitely in patients with a history of DVT or thrombophilia is indicated.[79,86] For non-thrombotic MTS, compression, antiplatelets or anticoagulants or both are used. There is no RCT comparing these antithrombotic strategies.[79,86,90–93] There are no comparative data between direct oral anticoagulants (DOAC) and warfarin in post-venous stenting.[86,94]

Finally, After successful iliac stenting; solving the leg venous hypertension, compression stockings are no longer needed.[95]

Diagnostic assessment and risk of overtreatment

As mentioned before, the exact incidence and prevalence of MTS are unknown and probably underestimated. Knowing that asymptomatic subjects with MT anatomy do not required treatment the diagnostic approach must be meticulous in order to avoid overtreatment.[96] Since the early 2000's some authors have emphasized this difference.

Kibbe et al, studied scans of 50 patients with abdominal pain and without any leg swelling or discomfort, they found compression greater than 50% in 24% of the patients, while in 66% compression greater than 25% was present, the mean age of the patients was 50 years. So, significant left common iliac vein compression is a frequent anatomic pattern in asymptomatic individuals.[14] There are several studies most of them retrospective reporting high technical success up to 98% and low complication rates with five years follow up from 0% to 20%[18,19,37,64,65]; but, in many patients symptom relief were reported inconsistently.[82,83,86] Previous systematic reviews showed relief of edema and pain in up to 64% to 68% and 82% of patients studied[96,97]; This suggests that more than one third of the patients could be overtreated.

More recently Van Vuuren et al, described a prospective, transversal research with 20 volunteer healthy patients 20 to 22 years old that underwent iliocaval venography with these results: 3 (15%) had narrowing of the common left iliac vein. In 16 (80%) at least two signs of MTS were present and in 1 (5%) none sign of obstruction was observed. Additionaly, the authors surveyed 30 vascular Experts, 23 of them (70%) considered iliac vein collaterals the most typical sign of chronic obstruction and more than 50% compression was found an indication to stent in 55% of healthy subjects; They concluded that overtreatment of MTS based just by venography is possible and advise to treat the patient rather than the image is a valid principle.[54] Actually, more than half of all Iliac vein stents implanted worldwide are for MTS[98–100] and, data on long term outcome and quality of life (QoL) are lacking. Van vuuren et al are running a prospective randomized trial single-blind study that will include 130 patients comparing conservative deep venous management to interventional treatment stratified for the PTS or MTS. The primary outcome is the QoL change after 12 months compared to base line QoL.[101] It is expected that this and others prospective randomized projects now in course will provide us data to optimized the management in this complex pathology.

Conclusion

After 60 years of MTS first publication, May-Thurner Syndrome, also known as May-Thurner-Cockett Syndrome or Iliac Vein Syndrome is better understood and as consequence a more appropriate and selective therapy indication will avoid the trend to overtreatment seen nowadays.

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Contributorship

RA and DA conceive the study and review literature, LD was involved in protocol development, RA, DH and ER wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the first version of the manuscript.

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