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May-Thurner Syndrome – Diagnostic and therapeutic dilemmas (RCD code: I-1D.2)

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Abstract

May-Thurner Syndrome is a rare vascular disease in which the right common iliac artery compresses the left common iliac vein. It occurs 5 times more often in women than in men, usually in their 20s and 40s. Patients suffer from deep vein thrombosis, post-thrombotic syndrome, and pulmonary embolism. They usually present with swelling of the left leg, chronic leg pain, skin colour changes, tingling and/or numbness of the affected limb, varicosities, phlebitis, and venous stasis ulcers. Available diagnostic tests include venous duplex ultrasound, computed tomography, magnetic resonance imaging, venography, and intravascular ultrasound. Endovascular therapy, including angioplasty, stenting, and catheter-directed thrombolysis is the current mainstay of treatment. Long-term anticoagulation and elastic compression stockings are used to prevent recurrent blood clot formation and decrease the risk of post-thrombotic syndrome. Thrombophilia screening is essential, as it would aid in the decision-making process regarding continuation of anticoagulant therapy. We present the case of a 38-year-old woman in her fourth pregnancy, presenting with persistent left leg oedema and recurrent deep vein thrombosis, eventually diagnosed with May-Thurner Syndrome. JRCD 2018; 4 (1): 22–25

Key words: rare disease, deep vein thrombosis, May-Thurner Syndrome, venous stenting, anticoagulation

Case presentation

A 38-year-old woman in her fourth pregnancy was diagnosed with left femoral deep vein thrombosis (DVT) during her 11th week of pregnancy. The patient reported pain and lower left limb oedema. Physical examination revealed the presence of bruising and oedema of the left lower extremity. Laboratory tests revealed elevated D-dimer level (6479 mg/ml) and normal values of haemoglobin (13.6 g/dl), Activated Partial Thromboplastin Time (APTT) (25.7 sec.), Prothrombin Time (PT) 10.9 sec., International Normalized Ratio (INR) 0.9, fibrinogen (393 mg/dl), and Antithrombin III (AT III) 80%. She was treated with a therapeutic dose of low-molecular-weight heparin (2x0.6 ml s.c An allergic reaction (thought to be connected with heparin treatment) and progression of thrombosis (common femoral vein and left iliac vein thrombosis in ultrasonography) was observed in her 23rd week of pregnancy (Body Mass index (BMI) 23.5 kg/m^2). After haematological and angiological consultations, treatment was changed to fondaparinux (1 × 2.5 mg s.c.). In her 29th week of pregnancy (BMI 27.65 kg/m^2), due to persistent complaints and an unchanged ultrasound image, the dose of fondaparinux was increased to 1 × 7.5 mg. This treatment was continued until labour (37th week of pregnancy – via caesarean section). After childbirth, the patient underwent work-up for thrombophilia. Genetic testing revealed 2 mutations in the Methylenetetrahydrofolate Reductase (MTHFR) gene (MTHFR c.665C>T-heterozygote and MTHFR c.1286A>T-heterozygote). After this diagnosis, the patient was treated with compression therapy and rivaroxaban (1 × 20 mg) (labile INR during warfarin treatment). Due to a persistent diameter discrepancy between the affected and unaffected limb (3–4 cm), Computed Tomography (CT) angiography was performed. It revealed left external iliac vein occlusion and well-developed collateral circulation. After consultation with the interventional radi-

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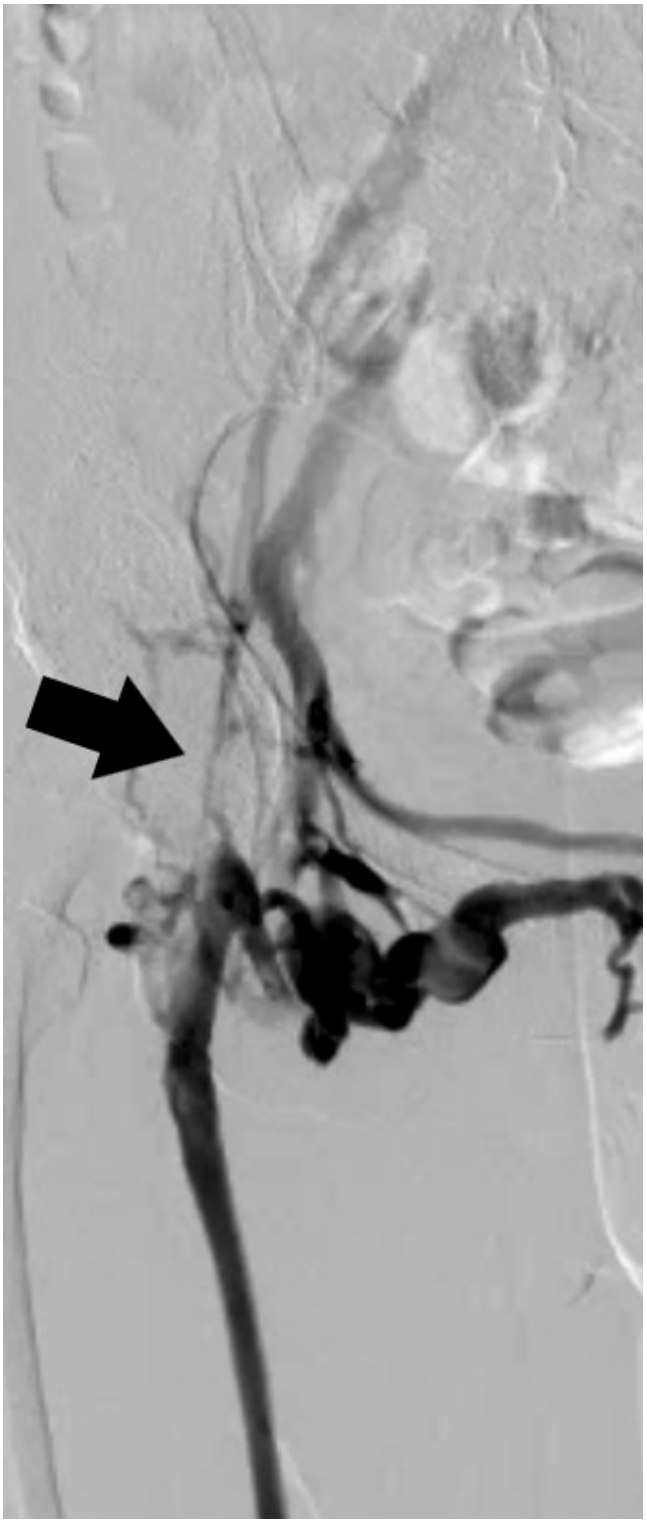


Figure 1. The left external iliac vein occlusion and well-developed collateral circulation

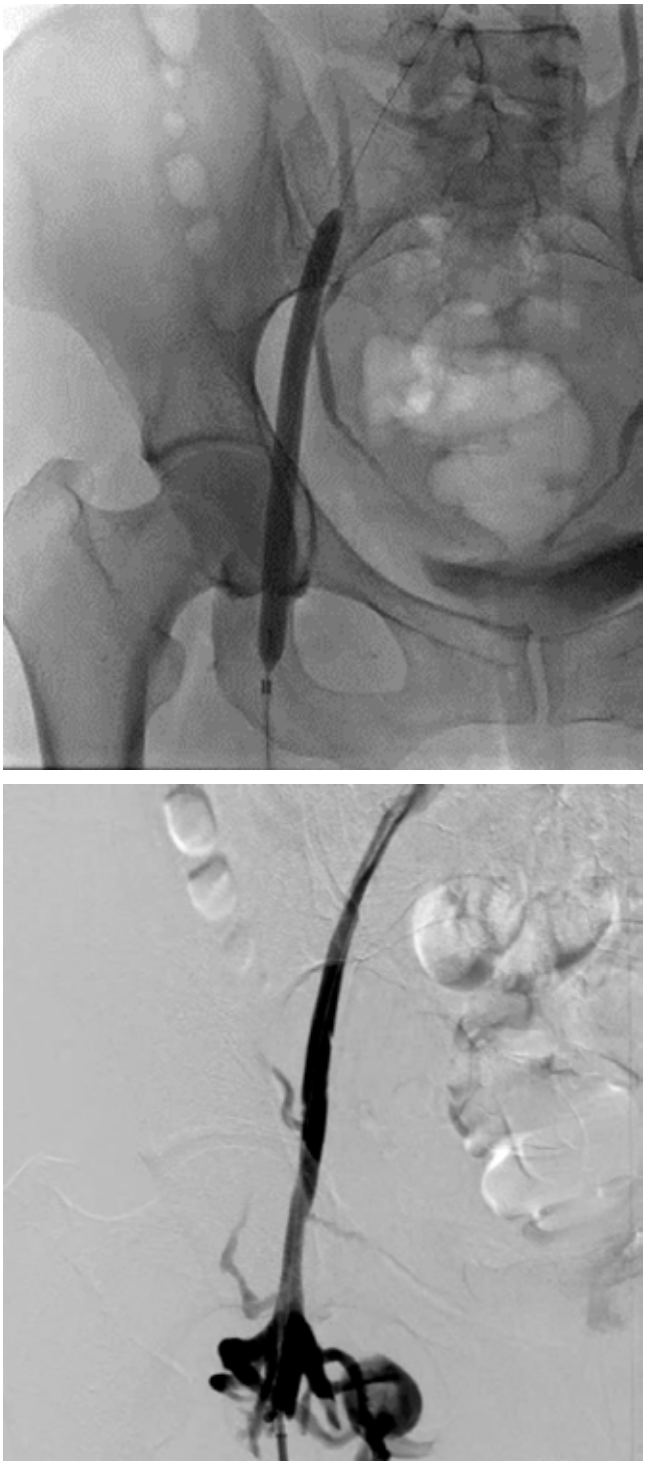


Figure 2. Balloon angioplasty

ologist, the patient was qualified for endovascular therapy. During the procedure, blood flow through the left external iliac vein was restored and two venous stents were implanted (ZILVER VEIN and WALLSTENT) On discharge, anticoagulation with rivaroxaban (1×20mg) was continued. Due to early recurrence of symptoms three weeks later, the patient underwent repeat interventional treatment. Restenosis of stents and signs of May-Thurner Syndrome (MTS) were observed in venography. A ZILVER VEIN stent was placed in the left common iliac vein, a WALLSTENT endoprosthesis was placed in the left superficial femoral vein, and a PROTÉGÉ GPS stent was inserted in the left external iliac vein. Due to suspicion of rivaroxaban ineffectiveness, the patient received anticoagulation with a vitamin K antagonist (VKA),

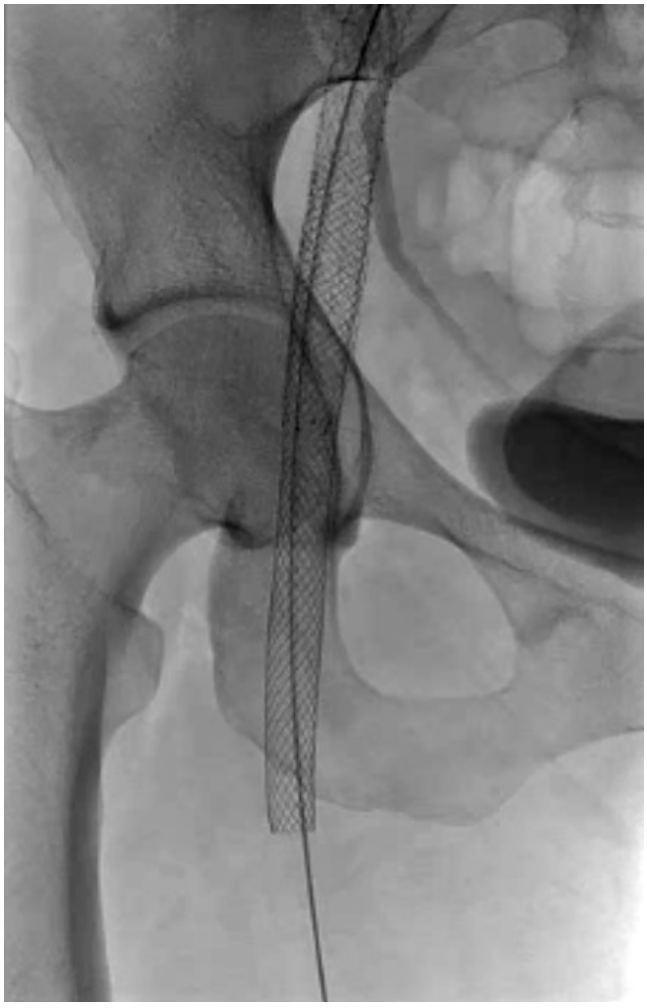
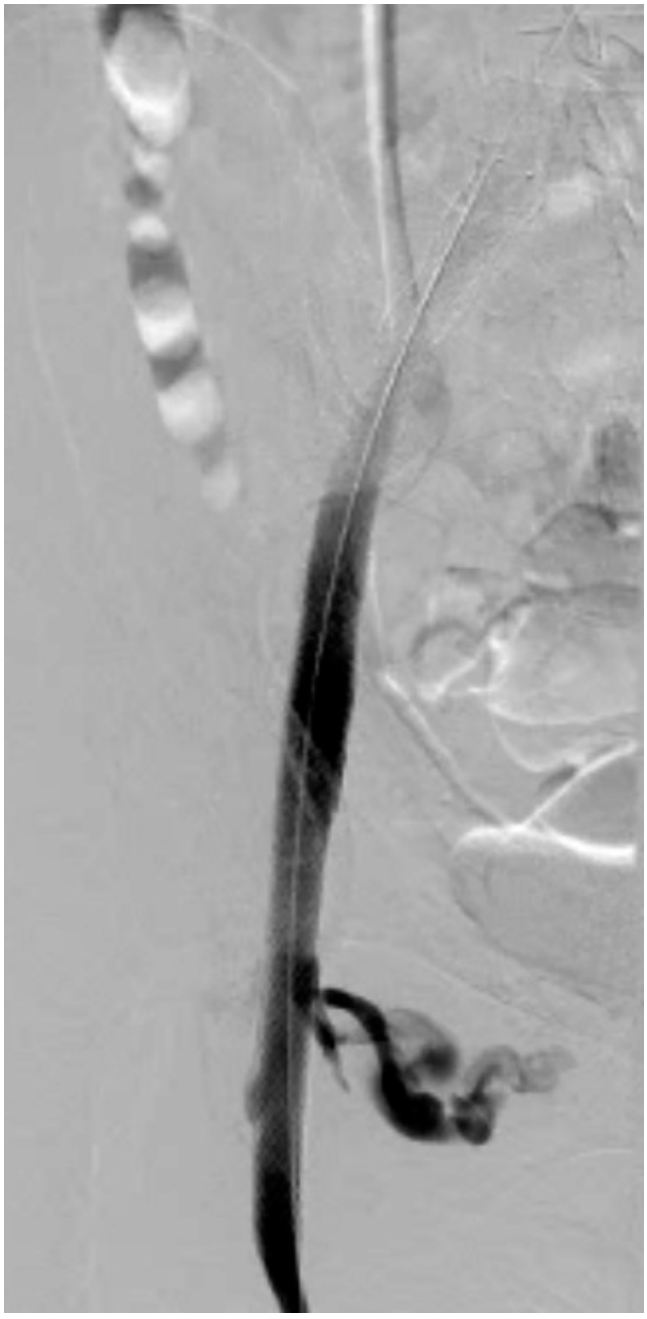


Figure 3. Venous stent implantation and final effect of the procedure

Acenocoumarol, upon discharge Currently, the patient suffers from minor oedema of the left calf Ultrasonography revealed a valvular failure of the left popliteal vein, while stents were patent. Despite following a controlled diet and avoiding medications which could affect VKA concentration, the patient experienced difficulties in maintaining a stable INR (fluctuations from 1.0 to 5.0, without bleeding or thrombotic complications). Treatment of this patient presents a real challenge, due to possible allergic reaction to low-molecular-weight heparin, high cost of fondaparinux, and inefficiency of rivaroxaban.

Review of literature

MTS is a rare vascular disease. It is estimated to be responsible for 2–5% of lower extremity venous disorders [1]. Other names for this disease include iliac vein compression syndrome, Cockett syndrome or iliocaval compression syndrome [1]. Its most common variant is caused by right common iliac artery compression of the left common iliac vein. It is thought to be present in up to 1/3 of the general population [2]. In the literature, other variants of this syndrome have been described, including compression of



the left common iliac vein by the left internal iliac artery, compression of the right common iliac vein by the right internal iliac artery, compression of the inferior vena cava by the right common iliac artery, and cases of right-sided MTS [3]. There are also cases of secondary MTS, where the left common iliac vein is compressed by the anteriorly translated lumbar spine [4].

The vast majority of patients with this syndrome have no symptoms [2,3]. Symptomatic MTS occurs 5 times more often in women, usually in their 20 s and 40 s [1,2]. Chronic pulsations of the overriding right iliac artery lead to collagen and elastin accumulation, extensive intimal hypertrophy of the vein, impaired venous return and ultimately to venous thrombosis [1,3]. Situations such as prolonged immobilisation, cancer, surgery, pregnancy, oral contraceptive use, dehydration, and infections may induce blood clot

formation, causing significant narrowing or complete occlusion of the vein [1-3]. Symptoms usually affect the left leg or pelvis. Patients suffer from DVT, post-thrombotic syndrome (PTS), and even pulmonary embolism (PE). They can present with oedema of the left leg, chronic leg pain, skin colour changes, hardening or thinning of the skin, tingling and/or numbness of the affected limb, varicosities, phlebitis, venous stasis ulcers, or phlegmasia cerulea dolens [1-3]. Typically, the entire affected leg is swollen – often it is considerably larger than the opposite leg [2]. In case of MTS suspicion, the first diagnostic test should be a venous duplex ultrasound [2]. However, due to its inability to visualise iliac vein compression, the relatively high and deep location of the iliac veins, a venous duplex ultrasound can be inadequate [2,3,6]. Direct visualisation of the pathology is provided by CT and magnetic resonance imaging (MRI). These non-invasive tests provide a final diagnosis, as well as revealing the DVT and its precise extension [1-3]. The gold standard for diagnosing MTS is venography. Together with intravascular ultrasound (IVUS), it is rather reserved for cases in which simultaneous treatment is planned [2,3]. The goal of MTS therapy is to restore normal blood flow, remove any possible clots, and to prevent further compression on the left iliac vein. Techniques such as angioplasty, stenting, and catheter-directed thrombolysis (CTD) with urokinase or tissue plasminogen activator (t-PA) have successfully been used to relieve acute symptoms and prevent the development of chronic symptoms associated with PTS [1-3,5,6]. When minimally invasive procedures fail, less common treatment options are available, including open surgical clot removal (thrombectomy) with repositioning of the right common iliac artery, various bypass procedures, excision of the intraluminal spur with patch venoplasty [1-3]. Taking into consideration that modern endovascular therapy, both independently and in combination with a surgical approach, is the mainstay of treatment in MTS patients, these less common options are rather historical techniques [5]. In long-term treatment, anticoagulation and elastic compression stockings are used to prevent recurrent blood clot formation and decrease the risk of PTS [1]. There are discrepancies about the duration of anticoagulation therapy after endovascular procedures and the role of antiplatelet therapy [7]. According to ACCP guidelines, anticoagulation therapy with VKAs should last at least 3 months in patients following deep vein thrombolysis and venous stent placement (with INR range 2–3) [7,8]. Despite these recommendations, treatment methods following these procedures highly vary. Although VKAs are the most commonly used agents, some experts use Direct Oral Anticoagulants (DOACs) with or without antiplatelet medication. Moreover, in the majority of vascular centres, the duration of anticoagulation therapy lasts at least 6 months [3,5]. According to the International Delphi Consensus, anticoagulation following DVT thrombolysis and iliac vein stenting can be discontinued after 6–12 months, if thrombophilia screening is negative, it is the first DVT, and the stent appears satisfactory on ultrasound [9]. Anticoagulation should be continued until end-of-life in patients with multiple DVT and iliac vein stenting [9]. According to a study by McBane et al., antiplatelet agents failed to prevent venous stent thrombosis, so they are not the preferred method of treatment [10]. This is due to the fact that venous thrombosis is primarily caused by increased thrombin generation and activity [11]. The incidence of re-thrombosis in stented patients ranged in different studies from 5% to 25% [7]. In MTS patients, a primary patency rate of 93%, an assisted primary patency rate of 97%, and a secondary patency rate of 99% after 3 years were revealed [12]. Despite the fact that no clear association between thrombophilia and MTS had been found, patient work-up for thrombophilia should be an essential requirement, as it could aid in decision-making regarding the continuation of anticoagulant therapy [5,9]. In our case, technical difficulties with obtaining optimal procedure effect might have caused early restenosis in the previously implanted stent.

Mutations in the MTHFR gene, found in our patient, increase homocysteine levels (unfortunately, in the patient, the level of homocysteine was not obtained). Hyperhomocysteinemia increases the risk of vein thrombosis (it activates coagulation factors V and VII, increases thrombin formation, and aggregation of platelets) and probably arterial thrombosis (high levels of homocysteine are correlated with strokes and heart attacks). Moreover, mutation in the MTHFR gene interferes with folic acid metabolism, increasing the risk of recurrent miscarriages and neural tube defects in infants [13].

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