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Diagnosis of May-Thurner Syndrome in a Case of Acute Pulmonary Embolism with Multiple Risk Factors: A Case Report and Review of Literature

Amy Belba

Trainee in Anesthesia and Intensive Care, KULeuven, Katholic University Leuven, Belgium

***Corresponding author**
Amy Belba, Trainee in Anesthesia and Intensive Care, KULeuven, Katholic University Leuven ,Belgium, E-mail:belbaamy@live.com

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Abstract

Background: *May-Thurner Syndrome (MTS) is aniliac vein compression syndrome which results in a thrombosis of the common left iliac vein. The main cause of this compression is the overlying right common iliac artery.*

Method: *In this article we describe the case of a 35-year-old woman with bilateral lobar pulmonary embolism (PE) together with an investigation of the risk factors leading to PE. The final diagnosis was a MTS with asymptomatic left internal vein thrombosis, further complicated by a PE.*

Results: *Precipitating factors were polycystic ovarian syndrome, combined oral contraceptives and a possible protein S deficiency.Treatment encompassed anticoagulation during the first year of treatment. Re-evaluation together with further retesting of protein S and imaging will determine the need for an endovascular approach to the iliac vein compression. In this article we discuss the diagnostic approach to patients with PE with an asymptomatic deep venous thrombosis.*

Conclusions: *This article seeks to draw attention to MTS as an incompletely studied syndrome which is potentially frequent in female patients with PE and interacts with other factors to increase the risk of a thrombosis. MTS should be considered in the differential diagnosis of a patient with PE in addition to patients presenting with a proximal deep venous thrombosis.*

Keywords: Deep Vein Thrombosis, May-Thurner Syndrome, Iliac Vein, Polycystic Ovarian Syndrome, Pulmonary Embolism, Combined Oral Contraceptives

Introduction

Venous Thromboembolism (VTE) is a common cardio-vascular disease with an incidence rateof 1 per 1000 person years which is composed of two entities: deep venous thrombosis (DVT) and pulmonary embolism (PE) [1]. Deep venous thrombosis (DVT) is typically considered to be the main cause of PE (>90% of the cases), however there is only in 30-50% of the cases a DVT diagnosed by compression venous ultrasonography (CUS) [1]. DVTs are thus underdiagnosed in cases of PE.

May-Thurner Syndrome (MTS) is a disease that leads to proximal DVTs in young females when more than 70 % compression of the left common iliac vein is achieved [2]. Pulmonary embolism (PE) may be the first presentation of a DVT. Guidelines for the diagnostic workup of a patient with PE include a hemodynamic assessment, a heart function evaluation, laboratory analysis including d-dimers, compression venous ultrasonography (CUS) for identification of a possible DVT and pulmonary angiogram. Computed tomographic (CT) venography is not a standard imaging technique used during the investigation of PE if there is no clinical suspected proximal DVT. Concluding, in female patients with PE there is a potentially important under diagnosis of proximal DVT.

The subject of this report is the case of a young female patient who presented in the Emergency Department with bilateral lobar PE. This case study includes the investigation of the interrelations between the present risk factors of PE as well as our findings on the possible pathogenesis of this case of PE. The paper contains relevant literature on the topics of PE; DVT; MTS; Polycystic ovarian syndrome (PCOS), an endocrine disorder with combined oral contraceptives (COC) as the first line treatment modality; COC's; and protein S deficiency, a subtype of inherited thrombophilia. The aim of this study is to present the diagnostic workup of this exceptional case of PE on the background of known PE risk factors. Our clinical question deals with the possible underdiagnosed of May-Thuner syndrome in the diagnostic process of patients with deep venous thrombosis and pulmonary embolism. To our knowledge this is the first reported case of MTS presenting with a PE and a proximal DVT without leg symptoms and evidence of DVT in CUS.

Material and methods

Case information was obtained from the patient record files of

the hospital. Patient anonymity was respected. General disease information was obtained from relevant literature.

The literature study included PubMed and Google Scholar searches for the most relevant peer reviewed articles reporting on PE, MTS, PCOS, COC and Protein S deficiency in the English language. Review articles and guidelines were screened for relevance and applicability to our casus. The following MESH terms were respectively used and combined: Pulmonary embolism, guideline; May-Thurner syndrome, asymptomatic, pulmonary embolism; polycystic ovarian syndrome, venous thrombosis.

Case presentation

A 35-year-old Caucasian female with a history of migraine and polycystic ovarian syndrome (PCOS) was admitted to the Regional Hospital Heilig Hart Leuven in the Emergency Department. The patient was taken in with shortness of breath, cough and a pain in the left thorax basis. The thoracal pain had persisted and increased for six days at the time of admission. The patient was fit with a normal BMI of 24. For more than a year prior to admission the patient had been treated with a combined oral contraceptive pill (COC), Daphne®, for her PCOS and oral Topamax® 50mg for migraine. No family history of VTE-, nicotine- or alcohol abuse was found.

On admission, physical examination revealed a severely dyspnoeic patient. Her heart rate was regular but tachycardia at 130, her room air oxygen saturation was at 98% with force decrease during limited effort and with a blood pressure of 130/85 mm Hg. The results of chest wall examination revealed normal bilateral vesicular respiratory sounds. The findings of heart and abdominal examinations were unremarkable, with no symptoms of DVTon examination of her legs and a bilateral negative Homans' sign.

In the Emergency Department, levels of serum electrolytes, glucose, blood urea, creatinine, and complete blood counts were normal. The arterial blood gas analysis with oxygen therapy revealed hypocapnia ($PaCO_2$= 26mmHg) and no hypoxemia (PaO2 =111 mmHg). Levels of D-dimer were elevated, reaching 1333 ng/ml. The chest X-ray was clear.CT pulmonary angiogram identified the presence of a bilateral lobarpulmonary thromboembolism (Figure 1). An electrocardiogram showed a regular rhythm consistent with sinus tachycardia. A CUS of the legs revealed no proof of an acute DVT in the patient's legs or higher venous system. A transthoracic echocardiogram revealed normal left ventricle function without a patent foramen ovale, an atrial septal defect or a ventricular septal defect, but with mild pulmonary hypertension (32 mmHg) and a tricuspid insufficiency grade 1/4.There was no evidence of shock or right ventricular dysfunction.

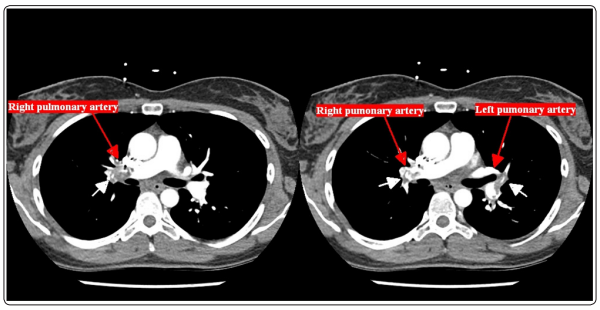
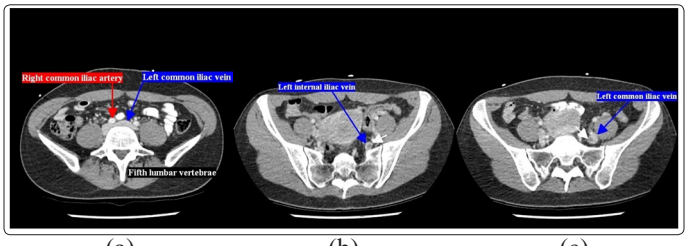


Figure 1: CTpulmonary angiogram showing bilateral lobar PE. White arrow: thrombosis in the left and right pulmonary artery

The diagnosis of pulmonary embolism was established based on the history and physical examination combined with laboratory testing and diagnostic imaging. The patient was hemodynamic ally stable and there was no evidence of cor pulmonale. Thrombolysis was thus not applied. The patient received standard anticoagulation treatment with enoxaparin (Clexane®), an unfractionated heparinand rivaroxaban (Xarelto®), an oral anticoagulant after a thrombophilia screening was performed. This included Protein S, protein C, Factor V Leiden and prothrombin G20210A.The combined hormonal pill was immediately stopped. Chest and epigastria pain was attributed to pleurisy, and was treated with acetylsalicylic acid (Aspegic®).

The patient was temporary hospitalised in the Intensive Care Unit for a period of four days for an intensive monitoring. The clinical status of the patient improved progressively. Control chest X-ray remained clear. Abdominal echography showed no abnormalities, indicating patency of vena cava inferior.

After resolution of the acute phase, the patient was hospitalised in the Cardiology Department. Control CT pulmonary angiogram revealed a favourable evolution with decrease in the previously described PE. Symptoms of headache led to a head resulting negative for bleeding, aneurysm or an embolic event. An electrocardiogram and transthoracic echocardiogram showed trends of normalisation of tachycardia and of pulmonary hypertension. Protein S deficiency was detected (44% with reference levels between 70% and 150%) which was to be reconfirmed at a future date. The rest of thrombophilia screening resulted negative. During the hospitalisation, a CT venography of the abdomen was planned in order to exclude a thrombosis of the proximal system and a pressuring mass. This last revealed a proximal DVT of the left internal iliac vein together with a compression of more than 50% of its diameter compared with the contralateral vein. A compression of this vein from the overlying artery, in other words the May-Thurner syndrome, was proposed as the underlying mechanism of the thrombosis (Figure 2). Presence of additional radiographic indicators of MTS like venous collateral and visible intraluminal spurs were not present. No pelvic mass was noted.



(a) (b) (c)

Figure 2: Abdominal CT venography: right common iliac artery crossing anteriorly to the left common iliac vein in (a) showing features consistent with the MTS. (b) and (c) demonstrate the thrombosis (white arrow) formed in the internal iliac vein extending to the common iliac vein distal to the compression by the right common iliac artery

After a total 12-day course of hospital treatment, she was discharged on rivaroxaban (Xarelto®), an oral anticoagulant. Further treatment of PCOS included a progestin-only pill (Lueva®). The patient's follow-up was performed by the Department of Cardiology, and we learned that the patient recovered well during two months post hospitalisation without any evidence of a recurrent DVT or other complications. The treatment will encompass one year use of oral

anticoagulation. Further diagnostic assessment will include a second measurement of free protein S for the diagnosis of a protein S deficiency and a control CT venography. The results will determine the need of further use of anticoagulation and the need of an iliac stent.

May-Thurner syndrome

Definition and pathogenesis

May-Thurner syndromeis an acute vein thrombosis of the left common iliac vein resulting from an external compression most frequently caused by the right common iliac artery [2]. The normal left common iliac vein has a relatively transverse course in respect to the right common iliac artery at the level of the fifth lumbar vertebrae (Figure 3). Its chronic compression and pulsation can result over time in endothelial damage, inducing changes both intraluminal (called spurs) and in the tunica intima, and a flow gradient [3]. These spurs are presumed to increase the risk of thrombosis providing two components of Virchow's triad (endothelial damage and hemodynamic changes)[3].Virchow was indeed the first who in 1957 observed a fivefold greater recurrence of DVT in the leftleg compared with the right [4]. May and Thurner in 1957 discovered the anatomical variation where the common iliac artery pressures on the common iliac vein in 22% of all examined cadavers [4].

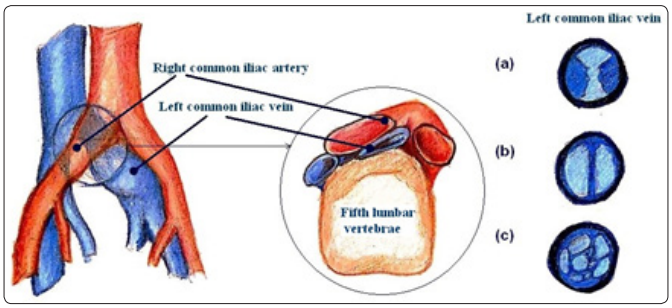


Figure 3: Left common iliac vein compression by the right common iliac artery. Changes in the left common iliac vein are demonstrated: (a) intraluminal spurs, (b) webs and (c) channels

Prevalence and clinical characteristics

The exact prevalence of MTS remains unknown. Iliofemoral thrombosis makes up 2-3% of all lower limb DVTs [3]. 50-60% of left sided iliofemoral DVTs exhibit iliac vein spurs resulting from intrinsic compression [3].The typical patient presenting with a MTS is a young female in the second to fourth decade of her life [3]. The syndrome may be also present in male patients but with a significant lower incidence. The classical symptoms are heat, pain, redness, and swelling of the affected leg, venous claudication, ulcerations, varicose veins and less frequently phlebitis, "phlegmasia Alba dolens" or "phlegmasia cerulean dolens".The clinical stages of the condition are delineated as Stage I, asymptomatic LCIV compression; stage II, the formation of an intraluminal spur; or Stage III, the occurrence of left iliac vein DVT [3].Patients with MTS present to the clinicians with typically symptomatic non-thrombotic chronic venous disease (chronic leg pain, chronic ulcers, or skin pigmentation changes)or acute DVT rarely complicated by a PE.

Diagnosis

There are no standard diagnostic criteria for MTS yet. Presently, the diagnosis of MTS is determined by both clinical and imaging indicators [3]. The primary radiographic indicator is a compression of more than 50% of the diameter of the left common iliac vein [3]. Additional radiographic indicators enclose venous collaterals, presence of intraluminal spurs, changes in the hemodynamic flow with the patient in supine position [3]. Other causes of iliac vein compression including trauma, postsurgical changes, pelvic masses, and radiation, must be excluded to diagnose MTS.

A number of imaging modalities have been used to evaluate the deep venous system among others trans-abdominal duplex ultrasound with unsatisfying results. The golden standard for radio graphically determining MTS is CT venography despite the fact that the results vary depending on the volume status of the patient [2]. A conventional CT inadequately captures an image with contrast on the arterial phase, not fully visualizing the venous system. CT venography is however not meant for routine use as there are not enough validation studies for detection of iliac vein lesions. Nuclear Magnetic Resonance technique shares the same problem and it is furthermore it is impossible for some patients to undergo it. In case of a stent placement, follow up is also impossible. Intravascular ultrasound is another valuable imaging in MTS. Considering its invasiveness, its use and the one of conventional venography is limited to cases where endovascular treatment is planned [5].

May-Thurner phenomenon

May-Thurner phenomenon is defined as the presence of compression of the common left iliac vein by the overlying right common iliac artery. This is considered to be an anatomical variant. 24% of an asymptomatic population shows a compression of more than 50% of the left common iliac vein [6]. For the compression to be thermodynamically significant a pressure gradient of more than 2-3 mmHg has to be measured over the compressed segment during contrast venography [3].This anatomic predisposition to DVT accompanied by other risk factors including hormonal treatment, immobilisation, smoking, pregnancy and hyper coagulation might lead to a proximal DVT. While evaluating the risk of DVT, there was no correlation between this risk and the degree of venous compression [6]. Concluding, this variant alone does not signify a higher risk for DVT and should not be treated during primary prevention of DVT [6].

Treatment

Guidelines for treatment of MTS are not available in the literature. We try to summarize in the following paragraphs general currently used treatments.

The primary treatment for ***acute DVT*** is anticoagulant therapy [2]. Treatment encompasses at least 3 months of anticoagulation for patients with DVT associated with a major reversible risk factor, at least 6–12 months of anticoagulation for patients with unprovoked or recurrent DVT, and long-term use of low molecular weight heparins for patients with cancer-related DVT [2]. Anticoagulation therapy alone is insufficient to prevent recurrence. Severely symptomatic patients are treated with catheter-directed thrombolysis together with stent placement and anticoagulation as first choice. Second choice treatment includes surgical venous thrombectomy. This treatment is applied when the first treatment is contraindicated [2]. The main purpose for the intervention is alleviating initial DVT symptoms, preventing early post-procedure thrombosis, preventing the post-thrombotic syndrome (PTS) and enables the healing of venous ulcers by removing the underlying venous outflow obstruction. Self-expanding arterial stents are generally used accompanied by anticoagulation for typically2 to 6 months.Results indicate that stent placement has a high technical success rate and it is effective

in restoring and maintaining patency in patients with MTS [7]. Stent placement risks include late re-thrombosis, re-stenosis, and migration (rare). Stents manufactured for venous blood vessels are currently in clinical trials. Temporary use of vena cava filter is justified for prevention of other PE [8].Its long term use is however inadvisable due to an increase in DVTs and no effect on survival [8].

Symptomatic non-thrombotic chronic venous disease on the other hand is treated with graduated compression stockings and with the treatment of venous insufficiency if present [2]. Severe clinical manifestations of this disease consisting of iliac vein lesion ranging from venous ulcers, to limb pain/swelling and concomitant saphenous vein reflux can be treated with stent placement. Another surgical treatment method meant for a more severe disease is the placement of a cross-femoral venous bypass graft named the Palma procedure.

Discussion

We encountered in the clinic young women with a May-Thurner syndrome complicated with PE but with no symptoms of DVT. The risk factors included PCOS, COC and a possible protein S deficiency.

Venous thrombosis is a multifactorial disorder and as such some patients might express more than one major risk factor.Thrombosis is regarded as 'provoked' when temporary or reversible risk factors (surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy) are present within the last 6 weeks to 3 months before diagnosis, and 'unprovoked' in the absence thereof [1]. Short-term treatment with anticoagulation is indicated for provoked VTE, long-term treatment should be considered for an unprovoked event. DVT, anatomically categorized into proximal DVT and distal DVT, is classically diagnosed with CUS. Proximal DVTs, involving proximal veins and the popliteal vein, are not easily visible with CUS and CT venography is better at detecting them. However since this last one is invasive, painful, and expensive and causing considerate radiation exposure it is limited to situations with a clinical suspicion of DVT but negative CUS. Diagnosis of a proximal vein thrombosis is important due to an increased recurrence rate compared to distal (calf) vein thrombosis. PE is an acute complication of DVT. Computed tomographic angiography has become the main thoracic imaging test for investigating suspected PE.

We could define this clinical case as a case of VTE where risk factors of provoked and unprovoked VTE interact with each other increasing the probability of a VTE. The identification of risk factors has implications on the late outcome and treatment options. In the acute setting, a conservative approach with anticoagulation was preferred considering that our patient showed no signs of acute thrombosis of the iliac vein. An invasive approach would lead to a high risk of an additional pulmonary embolism possibly causing hemodynamic instability. Cautious treatment with anticoagulation helped to bypass this critical moment and made a further investigation of the predisposing factors of VTE and of the possible treatment options.

Protein S deficiency (autosomal dominant) is an inherited thrombophilia related to a five to tenfold increased risk of thrombosis in family-based studies compared with controls [9]. Protein S deficiency, together with other inherited thrombophilia's, should be suspected in young patients (<40years) with a first PE/VTE especially in cases of unprovoked VTE as rates of thrombophilia disorders are high in this group [10]. Testing all patients with a first episode of VTE is not recommended [10]. Testing in the previously specified group of patients with VTE is necessary. Ideal cut-off levels of free protein S do not exist. Levels of free protein S used for the diagnosis in patients of this group are lower than 33 units/dl (corresponding with 33% free protein S)[9]. A diagnosis of MTS should always be accompanied with an evaluation of thrombophilia disorders, as Kolbel et al. found that 67%of patients with chronic iliac vein occlusion or MTS have some form of thrombophilia [11]. In the present case, protein S deficiency has to be reconfirmed before it is accounted as one of the risk factors. Erroneous estimation of protein S levels could be a result of treatment with estrogens (COCs) and the transient state of VTE [9]. These alternate the levels of free protein S leading to a transient acquired protein S deficiency whose clinical significance is unclear. The confirmation of this diagnosis requires that the test is redone while the patient is not anymore under influence of the affecting factors.

PCOS, a common reproductive and metabolic disorder, is associated with metabolic cardiovascular disease. Patients with PCOS are estimated to have a 1.5- to 1.9- fold increase in the prevalence of VTE compared with women without PCOS, regardless of PCOS phenotype and known risk factors (OCP use, region, diabetes, and obesity) [12,13]. Abnormalities in coagulation and a hypofibrinolytic state (among others increased PAI-1 levels and several pro inflammatory agents present in PCOS patients) lead to an increased risk of venous thrombosis. These characteristics of PCOS have not yet been fully explored [14].

Management of PCOS includes COCs as a first-line medical treatment. Potential adverse effects of COCs use are adverse metabolic and cardiovascular effects, including VTE (2- to 6-fold increased risk of VTE) [15]. In the vast majority of women, the benefits of COC use overweigh its risks. The effect of the combination of PCOS and its first line treatment (COC) on the risk of thrombosis is controversial. One study claims a diminished risk when COCs are used in PCOS patients compared to the risk derived from PCOS alone but the risk remains overall higher in PCOS patients than in the rest of the population [13]. The second study proposes a synergism between COC and PCOS, increasing the odds of VTE [12]. We advise that even though COC are the first choice medication for PCOS, an elaborate anamnesis is crucial to prevent cases of VTE considering the disputable evidence and the possible accumulation of risk factors leading to a VTE.

The diversity of the predisposing factors of VTE in this case of PE could disputably be sufficient to explain the occurrence of this phenomenon. It is questionable if further need of imaging was necessary. Nonetheless, the importance of diagnosis of MTS is evident in the fact that a missed diagnosis of VTE due to MTS results in an elevated recurrence of thrombosis, PE, and post-thrombotic syndrome with significant morbidity and mortality. While reading this data, the reader should be aware that MTS is typically symptomatic. Arguably the previous data could be extrapolated to a MTS with a symptomatic DVT in the affected leg but with a radio graphically present proximal thrombosis. The deriving question concerns the need of screening for MTS in patients with PE without symptoms and evidence of DVT in CUS. Previously fully investigated by a burdensome CT venography, broad investigation for a proximal DVT is presently regarded as superfluous. Many cases of MTS are thus probably currently not recognised. A DVT present in CT venography

and a compression of more than 70% of the vein confirms MTS. Nevertheless, absence of DVT does not exclude a previous loosely anchored thrombosis only symptomatic as a PE. Given that one fourth prevalence of at least 50% compression of the common iliac vein in these females, the question would further extends itself to the need of treatment of these patients with a stent.

Concluding, the diagnosis of May-Thurner is presently not actively investigated. The literature review stresses its importance in young females of typically the second to fourth decade. An increased risk of recurrence of thrombosis, pulmonary embolism and post-thrombotic syndrome accents its effect on this population indicating that more attention should be attributed to its diagnosis and treatment modalities. We think that a relatively frequent exposure to reversible risk factors, among others use of oral combined contraception, nicotine abuse in females and traveling by plane, might nowadays increase the significance of this underlying phenomenon leading to deep venous thrombosis in these females.

Conclusion

May-Thurner syndrome is a yet not fully investigated condition which arguably plays an important role in the prevalence of venous thromboembolism in females commonly of the second to fourth decade. Physicians must be vigilant with patients presenting with pulmonary embolism. A detailed investigation of the risk factors should be performed and May-Thurner syndrome should be considered even when multiple unprovoked and provoked risk factors are present. Protein S deficiency, together with other inherited thrombophilia's, should be suspected in young patients (<40years) with pulmonary embolism without a family history of thrombosis and in patients with May-Thurner syndrome. Polycystic ovarian syndrome patients have an increased prevalence of venous thromboembolism. The strongest evidence is present in patients having a polycystic ovarian syndrome with a metabolic phenotype. The effect of combined oral contraceptive use in patients with polycystic ovarian syndrome on thrombosis is controversial. Further studies are necessary to clarify this relation in order that recommendations can be created. To identify a possible May-Thurner syndrome and a proximal deep venous thrombosis an abdominal computer tomography should be considered among other radiological imaging. Finally, the overall contribution of this syndrome and its phenomenon on thrombosis is questionable. Additional research is required to determine its importance on thrombosis, bringing more clarity on the need of detection of this syndrome and the treatment alternatives.

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