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Endovascular Treatment of Deep Vein Thrombosis Associated with May-Thurner Syndrome: A Case Series

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Abstract Introduction: May-Thurner syndrome (MTS) is an entity caused by the compression of the left iliac vein that predispose to acute deep vein thrombosis (DVT) of left lower limb. While standar management is anticoagulant therapy, a review of the literature reveals that new endovascular therapies can offer more optimal outcome than anticoagulation alone, preserving normal venous valve function, and avoiding post-thrombotic syndrome. In addition, we have detected that the highest risk of complications appears when MTS is associated with another congenital or acquired prothrombotic factor (thrombophilia). Case presentation: We report four causes of MTS in caucasian patients treated with endovascular techniques in our hospital over the last years. All patients were middle-aged severe symptomatic women with positive venographic findings for acute or chronic extensive left lower-extremity DVT. In addition, all patients were positive for thrombophilia test. Conclusion: DVT study in patients with MTS must include a search for thrombophilia factors, as those patients are most likely to benefit from new technical approaches.

Keywords: *May-Thurner syndrome, iliac vein compression syndrome, venous thrombosis, endovascular therapy, stent, post-thrombotic syndrome, case report*

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1. Introduction

In 1957 May and Thurner described a fairly common anatomical variant, 22% out of 430 cadavers, in which the left iliac becomes trapped between the right common iliac artery and the L-5 vertebral body. The compression of the left iliac vein by the overlying right iliac artery, associated to this variant, is known as May-Thurner syndrome (MTS). The resulting mechanical trauma causes vein intimal hypertrophy and fibrosis. Endothelial membranes may form over time increasing the likelihood of venous stasis and thrombus formation [2]. Collateral circulation around the thrombus is also common.

The course of this condition may include recurrent unilateral pain with or without edema, varicose-vein development, and trophic changes to the skin [3]. When associated with other risk factors, chronic vein obstruction may even lead to deep vein thrombosis (DVT). Other major complications. like iliac vein rupture and disabling post-thrombotic syndrome (PTS), have also been described in patients with MTS [4].

MTS is currently considered an under diagnosed disorder, with most cases remaining unnoticed. Case series in the literature report that up to 25% of patients with DVT of the lower limbs can be associated with this anatomical variant [5, 6]. MTS is most likely to occur in women between the third and fourth decades of life. Awareness of this condition is therefore important. Especially for cases of iliofemoral DVT of the left leg showing poor response to treatment and in those patients without a clear predisposing or triggering trombotic factor [7].

Although current treatment for DVT associated with MTS is oral anticoagulant therapy (OAT), there is enough evidence in published case series showing the benefits of endovascular treatments., Stent placement or percutaneous balloon angioplasty (PTA) and pharmacomechanical thrombolysis can significantly reduce the rate of PTS and even achieve definitive thrombus resolution, specially in cases of extensive thrombosis with high risk of complications and recurrence [8,9].

2. Case Presentation

We report four causes of MTS in caucasian patients who were considered for endovascular treatment in our hospital during the last five years. All were middle-aged females with venographic findings indicative of acute or chronic extensive lower-lib DVT on the left side and severe symptoms (Table 1). In addition, three of them presented a positive thrombophilia study.

Case 1

A 32-year-old female with no significant medical history presented at the emergency department with a 3-day history of pain and edema of the left lower extremity

(LLE). Doppler ultrasound confirmed an extensive acute DVT from the popliteal vein to the left common iliac vein. The patient had no personal or family history of thrombosis, and use of estrogen-containing oral contraceptives (OCPs) was the only potential triggering factor. Anticoagulant treatment consisting of low-molecular-weight heparin (LMWH) adjusted to weight (enoxaparin, 80 mg every 12 hours) was immediately started. OAT with acenocoumarol was added 24 hours later. Heparin was maintained at the same dose until the fourth day, when the patient's INR came within therapeutic range (2.0–3.0). Despite a proper anticoagulant regimen, on the fifth day the patient returned to the hospital with persistent pain extending into the inguinal area and increased swelling. The heparin treatment was then re-initiated and OAT suspended. The acquired and congenital thrombophilia test were negative , including antithrombin, protein C and S deficiency, factor V Leiden (FVL), prothrombin 20210 gene mutation (PT 20210A), homocysteine levels, anticardiolipin Ig G and IgM, anti-β2 glycoprotein IgM and IgG and lupus anticoagulant. Just a low-positive antinuclear antibody (ANA), titer (1:80), was detected.

Table 1. Summary of reported cases of MTS

Case	Age	Sex	Thrombotic events	Location	Clinical sings	Doppler	Predisposing factor	Anticoagulant treatment
1	32	F	DVT	LLE	Pain and edema	Extensive DVT	OCPs	LMWH + OAT
2	59	F	DVT	LLE	-	-	OCPs	OAT (6 months)
			DVT-PE		-	-	Immobilization	OAT (3 years)
			DVT			Partial recanalization popliteal vein	PT20210A HT	OAT permanent
3	45	F	DVT-PE	LLE	Pain, edema, dyspnea	Extensive DVT	FVL HT	OAT (1 year)
4	41	F	DVT-PE	LLE			OCPs Air plane trip	OAT

Case	Age	Sex	Thrombotic events	Location	Complications	Venography	Endovascular treatment	Outcome
1	32	F	DVT	LLE	Persistent pain ↑ swelling	Acute thrombosis Collateral circulation Severe notchlike stenotic defect	Pharmaco-mechanical thrombectomy Preventive cava filter	Asymptomatic OAT
2	59	F	DVT	LLE	-	-	-	-
			DVT-PE		-	-	-	-
			DVT		PTS	Complete obstruction iliac vein Collateral circulation	Stent	Quality of life and local symptoms improved OAT
3	45	F	DVT-PE	LLE	PTS	Extrinsic compression common iliac vein (congenital origin) Collateral varicose veins	Stent	Improved progressively OAT
4	41	F	DVT-PE	LLE	PTS	Anatomic sings compatilble with MTS	No	OAT

In light of the poor response to medical treatment, a venogram was requested. Acute proximal DVT thrombus in the common femoral vein and the whole common iliac vein, with limited collateral flow from the branches of the deep femoral vein was found. A severe notchlike stenotic defect in the ostium of the left common iliac vein as the potential local triggering factor (MTS) was also discovered.

Based on the little initial improvement and the venographic findings a pharmacomechanical thrombectomy was done. From right internal jugular approach a retrievable inferior vena cava filter (Celect, Cook Medical, Bloomington, Ind) was deployed to prevent pulmonary embolism (PE) during thrombectomy procedure. The ipsilateral common femoral vein was punctured and an 8 F sheath was placed. After iv administration of 70 mg/kg IU of heparin a hydrophilic guidewire was advanced across the fresh iliac thrombus and across the stenotic ostium of the common iliac vein. A 7 F over the wire percutaneous thrombectomy Arrow-Trerotola device (Arrow, Reading, PA, USA) with simultaneous infusion of 300 000 units of urokinase was used to obtain the fragmentation and lysis of the iliac vein thrombus. Finally a PTA with a 12 mm catheter balloon was done to treat the iliac vein stenosis (Figure 1 and Figure 2).

In the 48 hours following the procedure the patient responded positively, exhibiting clinical improvement, relief of symptoms, and total resolution of the clinical signs of DTV. The vena cava filter was removed one month later.

After a follow-up of 36 months, the patient remains asymptomatic. Positive ANA results persist, with a mixed speckled and homogenous pattern and positive DNA antibodies (titer 70–90 IU/mL), normal complement levels, and no systemic signs of lupus. Due to these characteristics, the patient is undergoing follow-up in the Autoimmune Diseases Unit and is still in treatment with OAT.

Case 2

59-year-old female with unknown cardiovascular risk factors. She had suffered a first DVT in her LLE in 1984 related to the use of OCPs. In 1996 she experienced a second DVT, which was complicated by a pulmonary embolism (PE). That time, the event was associated with immobilization caused by a muscle strain. In September 2008, when she was no longer undergoing anticoagulant treatment, the patient presented her third episode in the left leg. She was then prescribed indefinite OAT. Thrombophilia screening revealed heterozygosity for PT20210A. In light of the poor response to treatment and the presence of substantial PTS (pain, increased size, and

trophic changes to the skin in the LLE), in 2009 the patient underwent a Doppler ultrasound scan of the area. It revealed a thrombosis with partial recanalization in the left popliteal vein. The venography showed a complete obstruction of the left primitive iliac vein with substantial post-phlebitic changes and collateral circulation in the hypogastric, lumbar, and vulvar veins. These findings were compatible with MTS. In February 2009, a self-expanding nitinol stent measuring 14 mm by 6 cm (S.M.A.R.T - Cordis, USA) was placed in her left common iliac vein. No vena cava filter was used in this case. During the first year postoperatively, a series of Doppler ultrasound examinations were performed to confirm stent patency. A substantial decrease in collateral circulation was seen, and LLE edema and pain were improved; however, the trophic changes to the skin remained. At present, her quality of life and local symptoms have significantly improved. Anyhow, the patient was prescribed permanent OAT due to her age, the positive thrombophilia test, and the substantial damage and sequelaes she had already undergone.

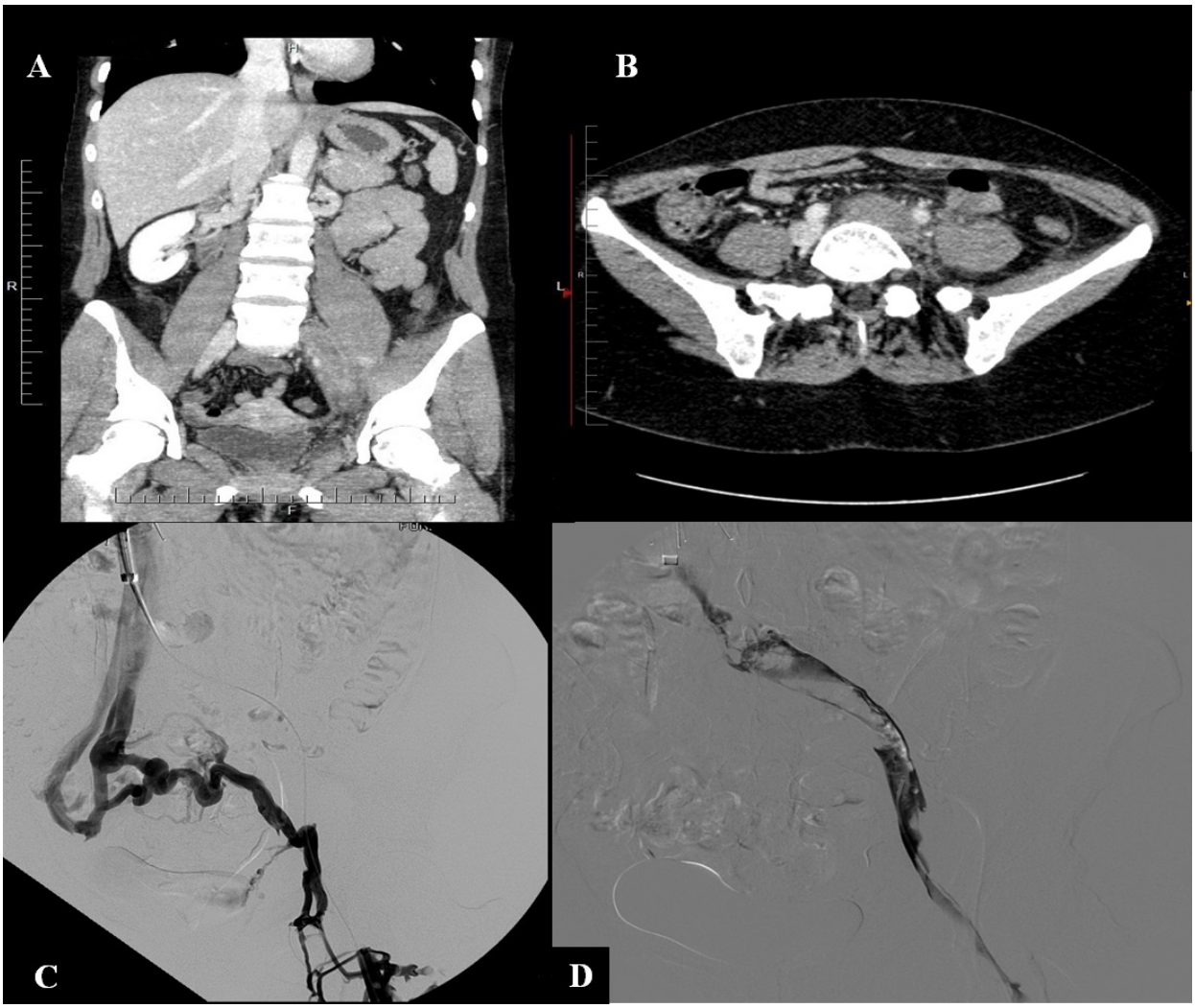

Figure 1. A: CT scan shows compression and thrombosis of left common iliac vein by right common iliac artery. Permeable flow can be seen in the right common iliac vein; B: venogram revealing thrombosis of the left iliofemoral venous system and the presence venous collateral flow from the left common femoral vein to the right hypogastric vein; C-D: pharmacomechanical thrombolysis. The thrombus was removed with an Arrow Trerotola PTD device and angioplasty. No stent was placed in this case. Subsequently, normal flow was restored

Case 3

In 2009, a 45-year-old female, who had undergone surgical treatment for a meningioma in 2008, presented with a 48-hour history of pain and increased edema in the left inguinal area. She associated also mild dyspnea. She had been taking OCPs for one month.. A venous Doppler ultrasound confirmed the clinical suspicion of extensive DVT, which continued up to the deep femoral vein. In addition, pulmonary arteries CT angiography verified the presence of a PE. Thrombophilia screening revealed the patient was heterozygous for FVL. Despite the substantial PTS and the persistent thrombus observed during the Doppler ultrasound follow-up examination, OAT with acenocoumarol was discontinued one year after. MR angiography and subsequent venography were performed, revealing extrinsic compression on the left common iliac vein. Post-phlebitic changes were observed in the left external iliac vein, appearing to be the cause of the collateral varicose veins in the pelvic and lumbar areas. All of these findings were, once again, compatible MTS.. In April 2013, due to the debilitating PTS and the large inguinal and suprapubic collateral circulation, an endovascular Zilver Vena (Cook, Bloomington, Ind, USA) 16-mm-by-6-cm self-expanding nitinol stent was placed. The patient continued receiving anticoagulant treatment with LMWH for one month postoperatively. At the time

of writing, the patient continues anticoagulant treatment and has improved progressively.

Case 4

This patient is a 41-year-old female who in 2010 had an initial DVT in the left leg associated with PE. Triggering factors included use of estrogen-containing contraceptives (vaginal ring) as well as several no long airplane trips the months before. The patient had no family history of thrombosis. Thrombophilia screening was negative. At the time of diagnosis, she was offered fibrinolysis with rTPA followed by intravenous perfusion of unfractionated heparin in another institution. Six years after the thrombotic episode, the patient, who presents anatomic signs compatible with MTS and mild PTS, continues receiving OAT with acenocoumarol. She was recently assessed in the Vascular Radiology Department, but she was not considered a candidate for immediate endovascular therapy due to the substantial chronic collateral circulation already present.

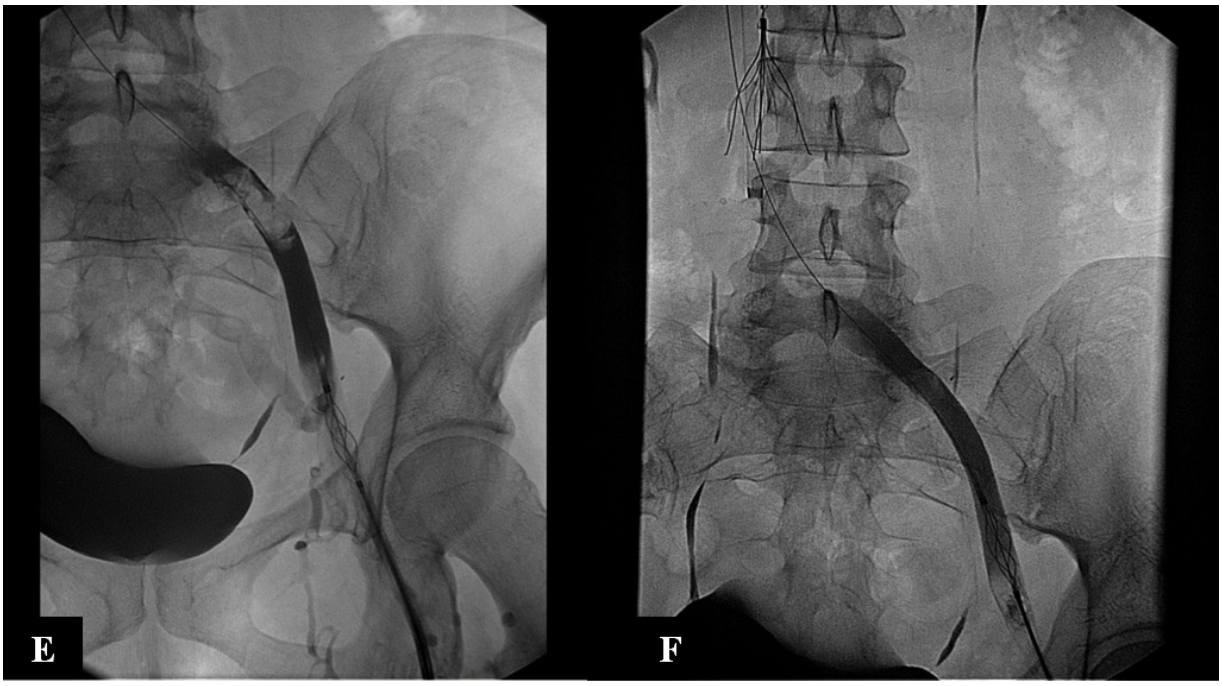

Figure 2. E-F: venogram shows resolution of thrombus and flow restored after thrombolysis in the left distal femoral and iliac vein. Small residual stenosis can be also seen

3. Discussion

Anatomic compression of the left common iliac vein by the right common iliac artery was first described by Virchow in 1851 [10]. However, a pathophysiological explanation of the consequences of prolonged compression on the vein and the flow of blood through it was not found until 1957, when May and Thurner carried out their study [11]. In 1965, Cloquett and Thomas, working with a series of 57 patients with extensive iliofemoral DVT, described the relationship between the anatomic alterations reported by May and Thurner and the presence of thrombosis in these patients [12,13]. The prevalence of MTS in patients with DVT is believed to be no more than 1% to 3% [6]. Some authors believe that only cases with clinical manifestations of MTS should be classified as such [14], since some consider the estimated incidence of the condition to be too high.

Due to the high likelihood of recurrence as well as the substantial number of post-thrombotic complications in these patients, initial clinical suspicion is crucial. It is especially important in middle-aged females (between the third and fourth decades of life) who present extended thrombosis in the LLE (above the popliteal vein and involving the iliac veins) with no clear triggering factor. Other possible causes of iliac compression, such as locoregional trauma, pelvic mass, or post-surgical changes, must be ruled out when treating these patients, Similarly, diagnosis must include a search for congenital and acquired thrombotic factors, as these cases have a greater risk of complications and recurrence. A previous history of superficial or deep thrombosis, edema or chronic pain in the left leg can guide the diagnosis. The gold-standard diagnostic test for these patients is venography; while CT and magnetic resonance could also be an option [15].

Historically, the treatment of choice for these patients has been OAT. However, it is known that OAT neither resolves nor prevents hyperplasia of the vessel wall and does not eliminate the existing membranes and synechiae [16]. In this regard, advances made in endovascular treatments such as pharmacomechanical thrombolysis, stent placement, or balloon angioplasty, represent new feasible options for the treatment of extensive proximal DVT in patients with MTS. It is known that when the compression of the left common iliac vein is >70%, the risk of recurrence and PTS is very high. Nearly 50% of patients with extensive DVT will develop PTS and up to 10% will have severe symptoms caused by the disorder [17,18,19]. According to recent publications, patients with MTS have a very high risk of recurrence, and up to 73% will have new events if no fibrinolytic treatment is administered [20], whether a stent is placed or not.

Berguer et al. were the first to describe catheter-guided thrombectomy and subsequent stent placement with these

patients [21]. Afterwards, many subsequent studies have been published, with very satisfactory long-term results [22, 23]. In 2002, Lamont et al. published a case series in which, after a 16-month follow-up, 80% of patients (12 of 15) remained asymptomatic following the procedure, and the remaining three presented only slight edema [8]. More recent series confirm these good results, indicating that the incidence of a new thrombotic event in patients with stents is low. Theses recurrences tend to occur in the first 3 months following the stent placement [24]. That is why close monitoring is advisable and should include venography testing throughout the first year [25]. Indefinite anticoagulant treatment appears not to prevent long-term physical damages in these patients. The more and more intensive therapies [26], such as direct catheter-guided thrombolysis with percutaneous mechanical thrombectomy [27], are being used. In fact, there is a lack of prospective data regarding the safety of the endovascular approach when compared with classic OAT. At present there is a promising multicenter, randomized controlled trial ongoing in the USA that aims to determine whether the routine use of pharmacomechanical catheter-directed thrombolysis in patients with acute proximal DVT reduces the risk of developing PTS (the ATTRACT Study) [28].

Endovascular approaches are not recommended in case of recent surgery or cardiovascular accident, severe hypertension, or high risk of bleeding. The potential complications of the treatments reported include risk of bleeding, PE, death (<0,4%) and stent thrombosis (few data published). In some series, up to 11% of patients present anaemia secondary to bleeding during the procedure, although major bleeding events us intracranial are rare,(<1%). On its behalf, PE can be prevented by the insertion of inferior vena cava filter in high-risk cases.

Regarding antithrombotic therapy after stenting, there is no strong evidence with which make general recommendations, and an individual approach should be considered. Some institutions prescribe anti-platelet treatment with aspirin or clopidogrel for a number of weeks after the insertion of the stent, but most data published concern coronary stents. In general, the trend is to avoid the use of anti-platelet treatment but to maintain the anticoagulant therapy (with warfarin or heparin) after stenting. The duration of this anticoagulant treatment is not clear and will depend on the risk factors associated, the presence of recurrence and de thrombus evolution. In general, the treatment must be administrated no less than 3 months. Current recommendations suggest discontinuing anticoagulant treatment after the procedure in well-monitored patients, after 6 months of anticoagulant therapy and with an image test that confirms stent patency [26,29]. However, more data and prospective clinical trials are required. In cases with thrombophilia, the decision of discontinuing the anticoagulant treatment remains still more complex. In these cases a long-term anti-platelet treatment may be contemplated if anticoagulant treatment is suspended.

4. Conclusions

In conclusion, most patients with MTS are asymptomatic; but, when accompanied by another prothrombotic factor, the likelihood of long-term physical damages related to DVT is very high. Initial clinical suspicion and use of diagnostic methods such as venography are crucial. From our point of view, in symptomatic cases with substantial compression of the left iliac vein and that present a positive thrombofilia study , the endovascular treatment -with or without stenting- should be consider as an option. There is some evidence that early thrombolytic intervention may reduce the risk of recurrence and decreases PTS. In high-risk patients with an extensive DVT, an endovascular approach could be considered as a first-line treatment. Even if it is done early, during the acute event, a pharmacomechanical thrombectomy without a stent positioning could be enough to reduce thrombus and prevent future events. In cases with recurrent thrombosis and presence of venous spurs and synechiae, stenting may be necessary.

In the absence of enough evidence and general guidelines, the final treatment indication for therapy should be individualized case by case, and based on the experience and resources of each health center. A multidisciplinary team, with the objective of offering the patient the most effective treatment and decreasing PTS, is advisable. More data based on prospective studies are necessary to make a solid recommendation about discontinuation of anticoagulant treatment.

Consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abreviations

MTS: May-Thurner Syndrome; DVT: deep vein thrombosis; OCPs: oral contraceptives; LMWH: low-molecular-weight heparin; LLE: left lower extremity; OA: oral anticoagulants; PT20210: prothrombine G20210A mutation; FLV: factor V Leyden; PE: pulmonary embolism; OAT: oral anticoagulant treatment; PTS: prothrombotic syndrome; DVT: deep vein thrombosis.

Competing Interest

The authors declare no conflict of interest.

Authors' Contributions

TAP carried out the selection of cases and review of medical records. She also drafted the manuscript. She was additionally responsible for the treatment and monitoring of patients. JUG was responsible for image diagnosis, endovascular treatment of patients and participated in the draft review. AGR participated in the review of the case histories and drafted the manuscript. PLS participated in the selection, treatment, and monitoring of cases. She coordinated and helped to draft the manuscript. All authors read and approved the final manuscript.

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