CASE REPORT

Unprovoked Upper Extremity Deep Vein Thrombosis in Patient with Primary Antiphospholipid Syndrome: A Case Report

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ABSTRACT

Upper extremity deep vein thrombosis is less common than in the lower extremity site. Such conditions can appear primarily or secondary to other conditions such as thrombophilia. One of the unique forms of acquired autoimmune thrombophilia is antiphospholipid syndrome (APS). We describe a 25 years old female admitted with sudden swelling, redness, and pain in her left arm. Venous ultrasound confirmed the diagnosis of thrombosis in the left subclavian vein, left axillary vein, left proximal brachial vein, and left proximal basilic vein. The patient was known to have a spontaneous miscarriage in the second pregnancy at eight weeks of gestation. Screening for autoimmune and antibody phospholipid was done, and primary APS was confirmed. She has been treated with a subcutaneous injection of fondaparinux 2.5 mg for five days and oral rivaroxaban 15 mg twice daily for 21 days. But four months later, the patient came with a thrombus in the subclavian vein due to inadequate treatment, then long-term treatment with vitamin K antagonist warfarin proceeded.

Keywords: APS, upper extremity, DVT

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INTRODUCTION

Upper extremity deep vein thrombosis (DVT) is an unusual site of DVT. Upper extremity DVT is about 1-4 % of all DVT in adults, with an incidence of 0.4–1.0/10.000 persons annually. About 20–30% of UEDVT are primary conditions, and the remaining are primarily secondary due to central venous catheter, cancer, and thrombophilia (Garcia et al., 2017; Mazzolai et al., 2018; Marshall & Cain, 2010). One of the unique forms of acquired autoimmune thrombophilia is antiphospholipid syndrome (APS). Antiphospholipid syndrome (APS) is a relatively common cause of venous thrombosis. Up to 20% of cases of deep vein thrombosis, with and without pulmonary embolism, may be associated with antiphospholipid antibodies (Farmer-Boatwright & Roubey, 2009; Sikara et al., 2011).

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder with a wide range of vascular and obstetric manifestations associated with thrombotic and inflammatory mechanisms orchestrated by antiphospholipid (aPL) antibodies. Common APS clinical features include venous thromboembolism, stroke, recurrent early miscarriages, and late pregnancy losses (Tektonidou et al., 2019). Anticoagulation with unfractionated heparin or low-molecular-weight heparin, followed by warfarin, is the standard of care. Longer term, the intensity and duration of warfarin anticoagulation necessary to prevent recurrent thrombosis in APS are essential issues (Farmer-Boatwright & Roubey, 2009).

The recurrence rate of thrombotic events among patients with APS is highly variable among studies, ranging from 0.5 to 20% annually (Finazzi et al., 2005; Girón-González et al., 2004; Ames et al., 2005; Okuma et al., 2010; Jackson et al., 2017). The recurrent rate is an increase in patients after a first unprovoked venous thromboembolism (VTE), and the anticoagulation was stopped. LA or triple aPL positivity is the leading risk factor for recurrence (Erkan & Zuily, 2019). Below we report a young female with recurrent upper extremity deep vein thrombosis secondary to primary antiphospholipid syndrome.

CASE REPORT

A 25 years old female patient who works as a nurse was admitted to the emergency unit with a complaint of gradual, sudden onset of heaviness, pain, and functional impairment of his left arm three days ago. The arm was cyanotic and swollen a week before, but the symptoms better within three days. But later, the symptoms arose; pain, redness, and cyanotic in the left upper extremity got worse when the patient lifted a heavy object, and the pain didn't relieve. She reported transient paresthesia of his left arm and cold in her left hand during overhead activities and could not perform repetitive or strenuous arm exercises. She has never had a history of accidents or intravenous catheter insertion. The patient has a spontaneous miscarriage at the

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8th week of gestation in the second pregnancy. There was no prior history of thrombosis, hypertension, hypertension, diabetes, cardiac, or blood disorder. There was no family history of thrombosis or other illnesses. The patient doesn't use any medication and has no history of smoking or contraception use.

The patient was alert with a blood pressure of 110/70 mmHg, pulse rate was 89 beats per minute, regular, sufficient amplitude, respiratory rate was 18 breaths per minute, and an axillary temperature was 37.1˚C. Examination of the extremities showed edema, redness, and pain in the left upper extremity and cold in the left hand.

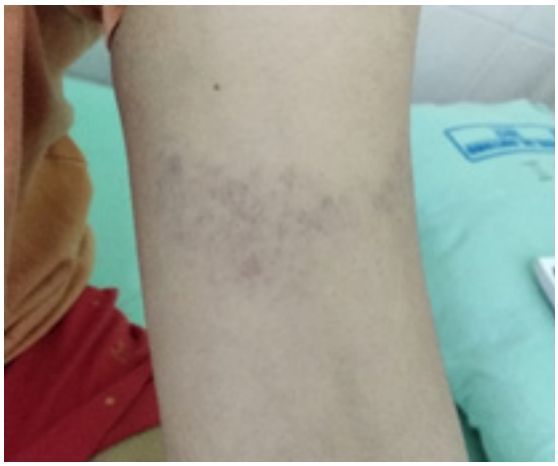

Figure1. The patient's clinical appearance showed edema and redness in the left upper extremity

Laboratory tests showed Hb 13.4 g/dl; HCT 41.4 %, WBC 9.030 /µL; neutrophile 75.7%, lymphocyte 16.8%, platelet count 256.000 / mm^3; AST 15 U/L, ALT 17 U/L, nonreactive HBsAg. BUN 12 mg/dl, SC 0.77 mg/dl and blood glucose 79 mg/dl. PPT 11.8 seconds (control:11.6), APTT 27.9 seconds (control 25.4). Electrolyte serum examination within normal limit, sodium 139.3 mmol/L, potassium 4.21 mmol/L, chloride 103.9 mmol/L. D dimer increase 1561.79 ng/mL. Urinalysis and urine sediment examination showed normal results. Chest x-ray and electrocardiogram show normal results.

The patient has been given methylprednisolone intravenous injection of 62.5 mg per day because of suspected autoimmune disease in the young female and warfarin 4 mg per day orally for suspect DVT. The patient was planned to perform a doppler ultrasound and anti-body anti-phospholipid due to a history of pregnancy morbidity. Venous ultrasound showed proximal brachial subcutaneous edema and thrombus that fulfilled the lumen of the left subclavian vein, left axillary vein, left proximal brachial vein, and left proximal basilic vein. The patient was diagnosed with left upper extremity deep vein thrombosis. Fondaparinux 2.5 mg was administered subcutaneously for five days, and rivaroxaban 15 mg twice daily for 21 days was planned.

Autoimmune and APL screening showed C3 103 mg/L (Normal: 50-120) C4 36 mg/dl (Normal: 20-50) ANAtest 14 units (Normal < 20), IgG anticardiolipin antibody (ACA) 2 GPL U/mL (Normal: < 12), IgM anticardiolipin antibody (ACA) 2 MPL U/mL (Normal: < 12), IgG Anti Beta 2 Glycoprotein 1 negative, dan IgM Anti Beta 2 Glycoprotein negative. Lupus antikoagulan (LA) 1: 122,2 second (Normal: 32-50 second), lupus antikoagulan (LA) 2: 63.9 second (normal: 29-37 detik), dan LA1/LA2 1.9 (normal: ≤ 1.2 detik). The patient was diagnosed with a primary antiphospholipid antibody with upper extremity deep vein thrombosis. Therapy was continued, and methylprednisolone was tapered to 16 mg three times daily orally.

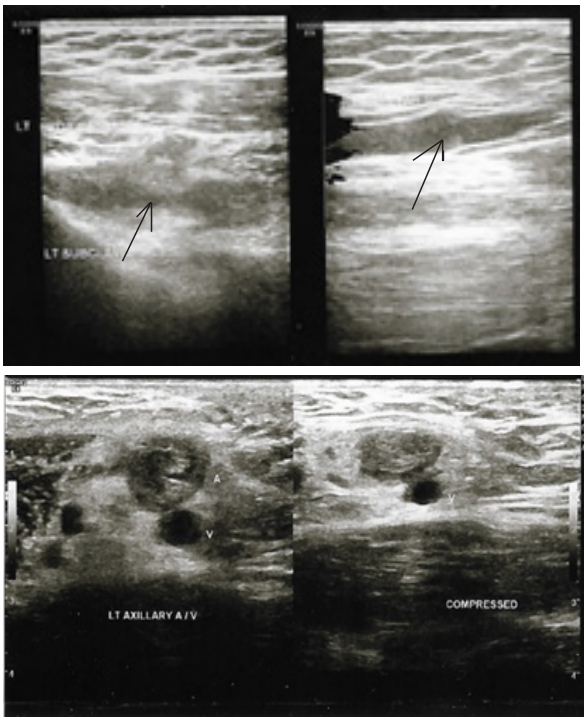

Figure 2. Venous ultrasound that show (from left to right) A. Thrombus on proximal basilic and subclavian vein B. Thrombus on left axillary vein C. Left axillar vein before compression D. Left axillar vein that uncompressible due to thrombus.

On the eighth day of admission, the redness of the left arm decreased, and the pain improved. Fondaparinux injection was completed, and the patient was planned to discharge with oral medication methylprednisolone 16 milligrams twice daily and will be tapered weekly. Rivaroxaban 15 mg twice daily was continued until 21 days and will be monitored. On the 21st day of rivaroxaban use, the patient came to the polyclinic with no complaint of pain and redness in the left arm, rivaroxaban was planned to be continued until three months, but the patient refused because she had no complaint.

Four months later, the patient came to the rheumatology polyclinic with pain and heaviness in the upper left arm. The patient was planned to check d-Dimer and venous ultrasound. Two weeks later, the patient came with a d-Dimer and a venous ultrasound result. D Dimer 142.06 and ultrasound show minimal thrombus in the left subclavian vein without flow limitation of the vein system. We suspected that were thrombus residues due to inadequate treatment. Warfarin 2 mg once daily for the long term was given.

DISCUSSION

Upper extremity deep vein thrombosis (DVT) consists of proximal and distal. Proximal upper extremity DVT is defined as thrombosis involving the axillary or more proximal deep veins, and distal upper extremity DVT is thrombosis of the brachial or more distal deep arm veins.

Axillary and subclavian veins are most frequently affected (Engelberger & Kucher, 2012). Upper extremity DVT is less common than lower extremity DVT for several reasons. The venous pathways of arms are less likely to form thrombosis than legs because of a relatively high flow rate and less stasis from gravitational effects. Even in bedridden patients, the upper limbs tend to be mobilized more than the lower limbs, resulting in less stasis. In addition, arm veins have fewer valves that can be foci of thrombus formation. The veins in the upper extremity are shorter and therefore have a lesser surface on which to form the clot. Moreover, arm veins have been shown to generate higher levels of plasminogen activator and fibrinolytic activity. In order to form upper extremity DVT, significant or extreme predisposing factors are necessary (Marshall & Cain, 2010).

Clinical Manifestations patients with upper extremity DVT typically present with heaviness, discomfort, pain, paresthesia, and swelling of the affected arm. Physical examination may find pitting edema, redness, or cyanosis of the involved extremity; visible collateral veins at the shoulder or upper arm; and fever (Mazzolai et al., 2018; Engelberger & Kucher, 2012). No validated integrated diagnostic strategy exists for upper extremity DVT encompassing the estimation of the clinical pretest probability, D-dimer testing, and imaging confirmation. A clinical prediction rule (Table 1)with or without D dimer examination was used, but this score is not too sensitive to be considered reliable (Engelberger & Kucher, 2012).

Table 1. Clinical Prediction Rule for Upper Extremity DVT

Clinical score item	Score
Venous material	+1
Localized pain	+1
Unilateral pitting edema	+1
Other alternative diagnosis	-1

Score characteristic

-1 or 0 = low probability patients

1 = intermediate probability patients

2 or 3 = high probability patients

D-dimer testing is not routinely recommended because most patients with suspected upper extremity DVT have elevated D-dimer levels because of comorbidities, recent procedures, or indwelling central venous catheters. Whereas venography remains the gold standard for diagnosing upper extremity DVT, color Doppler helps evaluate the proximal subclavian and innominate veins, where compression is impossible because of overlapping bony structures. Additional imaging tests may be required if the physiological variability of the Doppler flow velocity with normal respiration or with the Valsalva maneuver is reduced or absent. Both contrast-enhanced computed tomography and magnetic resonance imaging are helpful not only in confirming upper extremity DVT but also in diagnosing concomitant pathologies, including cancer, adenopathy, or anatomic abnormalities suggestive of the VTOS (Mazzolai et al., 2018; Engelberger & Kucher, 2012).

Upper extremity deep vein thrombosis may occur primary or secondary. Primary UEDVT is less common than secondary forms. The most common primary form is effort-related thrombosis, also called Paget-Schroetter syndrome. Most effort-related upper extremity DVT patients have an underlying venous thoracic outlet syndrome (VTOS). Secondary DVT includes venous catheter and devices-related complications, cancer, pregnancy, recent arm/shoulder surgery or trauma, immobilization of the arm, oral contraceptive use, thrombophilia, and ovarian hyperstimulation syndrome (Mazzolai et al., 2018; Engelberger & Kucher, 2012).

Antiphospholipid syndrome (APS) is a relatively common cause of venous thrombosis. Up to 20% of cases of deep vein thrombosis, with and without pulmonary embolism, may be associated with antiphospholipid antibodies (Farmer-Boatwright & Roubey, 2009). According to the revised Sapporo APS Classification Criteria, patients with definite APS at least fulfill one clinical and one laboratory criteria associated with other autoimmune diseases, mainly systemic lupus erythematosus (SLE) or its primary form (Tektonidou et al., 2019). The management of upper extremity DVT in a patient with APS aims to decrease symptoms, prevent progression of thrombosis, and reduce the risk of pulmonary embolism, recurrence, and PTS. Most recommendations for managing upper extremity DVT were derived from data from patients with lower-extremity thrombosis (Engelberger & Kucher, 2012).

In patients with definite APS and first venous thrombosis, EULAR recommends treatment with VKA with a target INR of 2–3 after initial therapy with unfractionated heparin (UFH) or LMWH bridging therapy of heparin plus VKA. Rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events. There is limited evidence about their effectiveness and safety in APS. Direct oral anticoagulants (DOACs) could be considered in patients unable to achieve a target INR despite good adherence to VKA or those with contraindications to VKA allergy or intolerance to VKA). In patients with provoked first venous thrombosis, therapy should be continued for a duration recommended for patients without APS according to international guidelines. Long-term use of anticoagulation is suggested in patients with unprovoked first venous thrombosis (Tektonidou et al., 2019).

Deep vein thrombosis treatment consists of three phases. Initial treatment (5–21 days following diagnosis); during this period, patients receive either parenteral therapy as bridging vitamin K antagonists (VKA) or use high-dose direct oral anticoagulants (DOACs). Long-term treatment (following 3–6 months); patients are treated with VKA or DOACs. Initial and long-term treatments are important for DPT patients with APS. The decision of extended treatment (beyond the first 3–6 months) is based on the benefit/risk effect of continued anticoagulation. In patients with severe renal failure (creatinine clearance <30 mL/ min), unstable renal function, or high bleeding risk, i.v. Unfractionated heparin (UFH) may be preferable (short half-life and protamine sulfate reversibility). UFH is associated with an increased risk of heparin-induced thrombocytopenia. For these reasons, low-molecular-weight heparin (LMWH) is the treatment of choice. LMWHs are as effective as UFH and safer. Fondaparinux can also be used as a parenteral agent. Both LMWH and fondaparinux do not have a specific antidote. Recently, DOACs have emerged as valid options

for DVT treatment. Dabigatran and edoxaban were studied following the initial 7–9 days of treatment with a parenteral agent. Apixaban and rivaroxaban were evaluated by the 'single drug approach' DOACs have longer elimination half-lives than UFH or LMWH. They may accumulate in patients with suboptimal renal (creatinine clearance <30 mL/min) or hepatic function (Child-Pugh class B or C). DOACs are at least as effective and probably safer than parenteral drug or VKA treatment (Mazzolai et al., 2018).

Fondaparinux can be used as an alternative to LMWH. Fondaparinux is an acceptable anticoagulant for most nonpregnant patients with newly diagnosed VTE. Fondaparinux is typically dosed according to patient weight as 5 mg once daily (<50 kg), 7.5 mg once daily (50 to 100 kg), and 10 mg (>100 kilograms). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance (CrCl) in the range of 20 to 50 mL/minute. No dosage reduction is required for patients with mild renal impairment (CrCl >50 mL/minute) (Lip & Hull., 2016).

Thrombosis in a patient with APS has a high rate of recurrent. Long-term use of anticoagulation is suggested in patients with unprovoked first venous thrombosis and sometimes indefinite in some patients (Erkan et al., 2019). Vena cava filter may be used when anticoagulation is contraindicated in patients with newly diagnosed proximal DVT. One major complication is filter thrombosis. Therefore, anticoagulation should be started as soon as contraindications resolve and the retrievable filter rapidly removed. Filter placement and anticoagulation do not improve survival except in patients with hemodynamically unstable PE or after thrombolytic therapy. Increased DVT recurrence has been shown with permanent but not retrievable filters (Mismetti et al., 2015; Stein et al., 2012).

Compression is used with the goal of compression to relieve venous symptoms and may prevent PTS. Although the role of elastic compression stockings in PTS prevention may be uncertain, their use remains a reasonable option for controlling symptoms of acute proximal DVT. Compression associated with early mobilization and walking exercise has shown significant efficacy in venous symptom relief in patients with acute DVT. Caution should be used in patients with severe peripheral artery disease (Kahn et al., 2014; Partsch & Blättler, 2000). The prognosis for patients with antiphospholipid syndrome (APS) depends on the clinical manifestations that lead to a diagnosis. For example, the prognosis is a poor inpatient at the initial episode, especially if presents with the multisystem disease as seen in catastrophic APS (Erkan et al., 2019).

SUMMARY

Upper extremity DVT is a less common form of DVT than lower limb DVT. It can be primary or secondary form but mostly secondary form. Venous ultrasound still becomes the standard diagnosis, but another imaging may be required if the location is complex or to confirm other underlying diseases. APS is the common acquired cause of venous thrombosis. DVT in patients with primary APS has a high recurrent rate, so long-term use of anticoagulation was recommended.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

AUTHOR CONTRIBUTION

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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