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UPPER ARM DEEP VEIN THROMBOSIS IN A PATIENT WITH ACTIVE LUPUS

Mahmoud Farouk Kamel Hassanein[1], Alaa Ebrahim[1], Stephanie Alcine Joseph[1], Teresa Jack[1], Ramprasath Anbazhagan[1], Miguel Fernández Olivares[2], Olena Kovalska[3]

[1] Department of Internal Medicine, Seychelles Hospital, Healthcare Agency, Victoria, Seychelles
[2] Nephrology Division, Seychelles Hospital, Healthcare Agency, Victoria, Seychelles
[3] Radiology Department, Seychelles Hospital, Healthcare Agency, Victoria, Seychelles

Corresponding author's e-mail: mahmoud.fkhassanein@health.gov.sc

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ABSTRACT

Upper extremity deep vein thrombosis (UEDVT) is relatively rare, and much less as an initial presentation of systemic lupus erythematosus (SLE). Primary UEDVT should be considered in individuals with unilateral arm swelling where the brachial, axillary, and subclavian veins are frequently involved. SLE is a chronic autoimmune disease that predominantly affects women of childbearing age and of African descent. Patients present with clinical features ranging from arthritis and arthralgias (over 90% of patients with SLE) to life-threatening hematologic, or central nervous system involvement. Individuals have an increased risk of arterial and/or venous thrombosis where the most important risk factor is the presence of antiphospholipid antibodies. Even within this condition, thrombotic events are typically seen in the legs, and UEDVT remains an unusual presentation. Here, we present a case of a 36-year-old female of African descent with a recent medical history of small joint arthralgia and vaginal bleeding due to uterine fibroids, for which she was prescribed a short course of prednisolone and norethisterone, respectively. She presented with a 2-week history of unilateral swelling in the left arm. Doppler ultrasound and later computed tomography scan with contrast indicated left UEDVT. Further investigations throughout her admission led to the diagnosis of SLE, while antiphospholipid syndrome - a common contributor to thrombosis in SLE - was notably ruled out. The patient was initiated on anticoagulants. The patient went on to later rapidly develop lupus nephritis and started on high-dose prednisolone. Given the high risk of bleeding, the decision to postpone the kidney biopsy was taken. There is limited data available about UEDVT when compared to lower extremity DVT and even fewer studies on SLE patients with thrombosis in the absence of antiphospholipid syndrome. Keeping this in mind, clinicians need to recognize idiopathic UEDVT as a potential early sign of SLE and maintain a high level of suspicion.

KEYWORDS

Upper extremity deep venous thrombosis, systemic lupus erythematosus, lupus nephritis, antiphospholipid syndrome, Paget-Schroetter syndrome

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LEARNING POINTS

- To highlight the possibility of idiopathic upper extremity deep vein thrombosis (UEDVT) in spontaneous unilateral arm swelling.
- Idiopathic UEDVT might indicate a serious underlying autoimmune condition as SLE in this case (in the absence of antiphospholipid syndrome), that requires intensive thorough investigation by a multidisciplinary team.
- Initial treatment of both UEDVT and lupus nephritis with standard dose anticoagulants and steroids might be the proper initial management, whereas kidney biopsy might not be necessary as the risk of bleeding is high while on anticoagulants.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease with unknown aetiology, but hormonal and genetic predisposition are considered likely etiological factors. Typical clinical manifestations include arthritis, a malar rash, and constitutional symptoms. On average, Hispanics and those of African descent are diagnosed with SLE at a younger age and with more severe forms of the disease than Caucasians[1]. The risk of thrombosis, which is higher in this population, is further increased in the presence of acquired pro-thrombotic factors such as corticosteroids or norethisterone use, as in this case, both adding to the prothrombotic milieu. Upper extremity deep vein thrombosis (UEDVT) as a clinical manifestation of SLE is relatively rare, much less preceding its diagnosis. UEDVT represents solely 4-10 percent of all cases of DVT[2]. Coon and Willis classified UEDVT as traumatic (caused by external stress or central venous cannulation) and spontaneous (associated with cancer or idiopathic)[3]. Others classify the condition as primary (idiopathic, Paget-Schroetter syndrome) and secondary (venous catheter, cancer, surgery, etc.). This case highlights the importance of suspecting an underlying autoimmune condition in the presence of UEDVT and also recognizing a broader range of prothrombotic factors in SLE beyond antiphospholipid syndrome (APS), even in unusual presentations like idiopathic UEDVT.

CASE PRESENTATION

A 36-year-old Seychellois woman of African descent was referred to the internal medicine department in June 2024 following a 2-week history of pain and swelling in her left arm. She denied any history of trauma to the affected area. Her medical history was notable for heavy menstrual bleeding (HMB) due to a subserosal uterine fibroid, managed with norethisterone under gynaecological follow-up. She was also being monitored for ureteric calculi and essential hypertension. She had no personal or family history of venous thromboembolism (VTE) or coagulopathies. She had previously attended a local clinic for polyarthralgia in the small joints of her hands. Upon presentation, she reported painless, unilateral swelling in her left arm. She denied experiencing chest pain, palpitations, dyspnoea, or fever. She also noted a similar episode of painless swelling in her left thigh 2 weeks prior. Physical examination in the emergency department (ED) revealed a firm, non-tender swelling of the left arm. A Doppler ultrasound of her left arm and leg revealed increased size, non-compressible brachial and basilic veins consistent with UEDVT and superficial venous thrombosis in the left arm. A Doppler ultrasound of her left leg showed no signs of DVT. The patient was admitted to the internal medicine department for anticoagulant treatment of UEDVT and further investigation. A contrast-enhanced

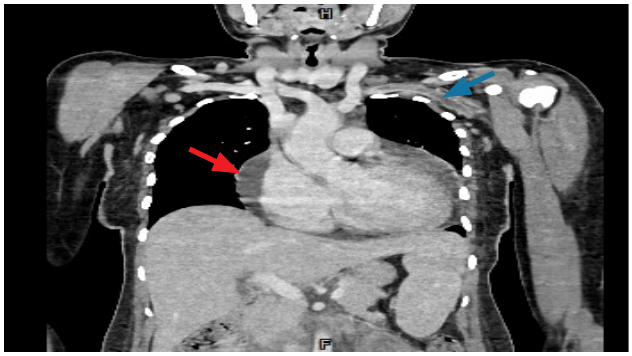

Figure 1. Coronal CT scan shows left axillary vein and left subclavian vein thrombosis (blue arrow) and pericardial effusion (red arrow).

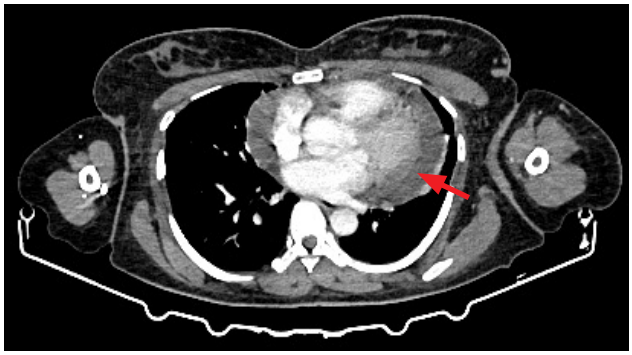

Figure 2. Axial CT scan shows pericardial effusion (red arrow).

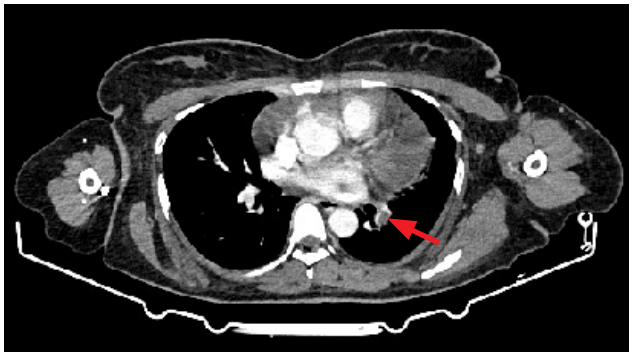

Figure 3. Axial CT scan shows a left lower lobe pulmonary artery embolus (red arrow).

Parameters	Results
Anti-CCP	Negative
ANA	Positive
ds-DNA	Positive
Antiphospholipid IgG	Negative
Antiphospholipid IgM	Negative
Anti-cardiolipin IgG Ab	Negative
Anti-cardiolipin IgM Ab	Negative
Complement	Low
Protein C	Normal
Protein S	Normal
D-dimer	Elevated

Abbreviation: CCP, cyclic citrullinated peptide; ANA, antinuclear antibody; ds-DNA, double-stranded deoxyribonucleic acid; Ab, antibody; Ig, immunoglobulin.

Table 1. Immunological and hereditary thrombophilia profile.

computed tomography (CT) scan of her neck and chest was performed to rule out thoracic outlet compression or other anatomical abnormalities. The scan confirmed UEDVT, with thrombosis of the left axillary (LAV) and left subclavian veins (LSV) *(Fig. 1)*. Additionally, the CT scan revealed pericardial effusion *(Fig. 2)*, a left lower lobe pulmonary artery embolus *(Fig. 3)*, a uterine fibroid with central necrosis, moderate non-specific hepatomegaly, mild diffuse small bowel wall thickening (suggestive of enteritis), and ascites. Further investigations during her admission led to a diagnosis of SLE *(Table 1)*. Autoimmune screening showed positive results for antinuclear antibodies (ANA) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA), while antiphospholipid syndrome, a common cause of thrombosis in SLE, was ruled out by negative results for antiphospholipid antibodies (IgM 2.51 U/ml, IgG 3.81 U/ml) and anti-cardiolipin antibodies (IgM 2 U/ml, IgG 2.15 U/ml). Complement levels were tested, revealing a normal serum level of C4 (40 mg/dl) and decreased C3 level (67 mg/dl). Given her history of polyarthralgia, anti-cyclic citrullinated peptide antibodies were also tested, yielding negative results and ruling out rheumatoid arthritis. Routine blood tests showed anaemia, with a haemoglobin level of 6.5 g/dl. Kidney function tests showed an elevated creatinine level of 121 µmol/l and serum urea of 7.8 mmol/l. The patient's coagulation profile revealed a positive D-dimer of 3.10 µg/ml. An electrocardiogram (ECG) showed sinus tachycardia, while an echocardiogram showed circumferential non-tamponading pericardial effusion *(Fig. 4)*.

During her hospital stay, the patient was started on prednisolone 40 mg/day, enoxaparin, warfarin, and hydroxychloroquine plus losartan and amlodipine for hypertension. After the resolution of her symptoms and stabilisation of the international normalised ratio at 2, she was discharged from the ward as a case of UEDVT with newly diagnosed SLE. Later on, she was seen in the general medicine clinic, where she reported having bilateral lower limb oedema, she kept having elevated creatinine levels. She was subsequently referred to the nephrologist for further evaluation, with creatinine levels rising to 155 µmol/l, urea to 23.4 mmol/l, and a 24-hour urine protein value of 2.91 g establishing the diagnosis of lupus nephritis. Due to the high bleeding risk associated with anticoagulant therapy, a kidney biopsy was postponed. The prednisolone dose was increased to 60 mg/day to be tapered down to 10 mg/day over a period of 3 months, hydroxychloroquine was continued, and mycophenolate mofetil 500 mg twice daily was added. Anticoagulation therapy with warfarin was continued, and over time, her kidney function and DVT symptoms improved with a reduced creatinine level to 75 µmol/l and serum urea to 7.7 mmol/l and a 24-hour urine protein value of 440 mg. A follow-up echocardiogram showed almost complete resolution of the pericardial effusion. Two months after discharge, the patient visited the general medicine outpatient clinic with a discoid rash over both upper extremities. Four months later, an outpatient follow-up CT scan confirmed the resolution of the DVT and lupus-related complications, with findings indicating a resorbed thrombus in the left axillary and subclavian veins, resolution of ascites, normal cardiac size with complete resolution of the

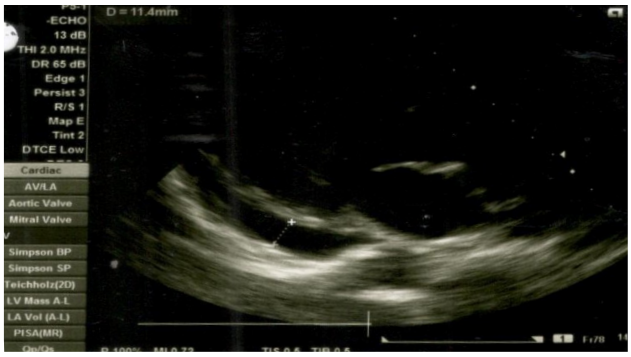

Figure 4. Echocardiography image showing pericardial effusion of 11.4 mm.

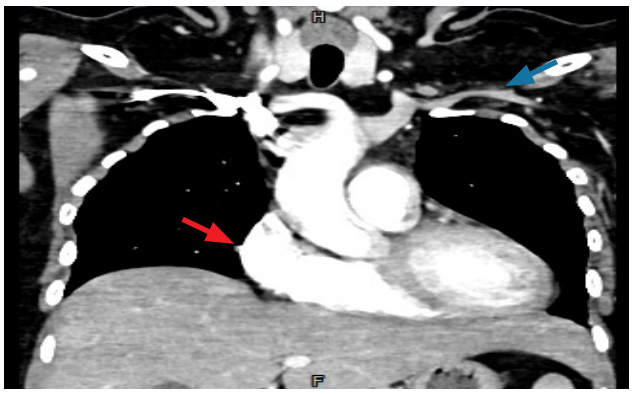

Figure 5. Follow-up coronal CT scan after 4 months of treatment, shows resorbed thrombus (blue arrow) and pericardial effusion (red arrow).

The entry criterion is necessary to classify SLE		
Entry criterion: • ANA at titre of ≥1:80 or positive test		
At least 1 clinical criterion required to classify SLE. Additional additive (clinical or immunology) criteria are counted toward the total score.		
1. Clinical criteria:	*Criteria score*	*Patients score*
Constitutional Fever	 2	 0
Haematologic Leukopenia Thrombocytopenia Autoimmune haemolysis	 3 4 4	 0 0 4
Neuropsychiatric Delirium Psychosis Seizure	 2 3 5	 0 0 0
Musculocutaneous Nonscarring alopecia Oral ulcers Subacute cutaneous or discoid lupus Acute cutaneous lupus	 2 2 4 6	 0 0 4 0
Serosal Pleural or pericardial effusion Acute pericarditis	 5 6	 5 0
Musculoskeletal Joint involvement	 6	 6
Renal Proteinuria >0.5 g per 24 hours Renal biopsy Class II or V lupus nephritis Renal biopsy class III or IV lupus nephritis	 4 8 10	 4 0 0
2. Immunology domains and criteria:		
Antiphospholipid antibodies	2	0
Complement proteins Low C3 or Low C4 Low C3 and low C4	 3 4	 3 0
SLE specific antibodies Anti-dsDNA Ab or anti-Smith Ab	 6	 6
A total score ≥10 and ≥1 clinical criterion is required to classify SLE		
Total score		**32**

Abbreviation: ANA, antinuclear antibody; SLE, systemic lupus erythromatosus; ds-DNA, double-stranded deoxyribonucleic acid; Ab, antibody.

Table 2. 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE.

pericardial effusion, normal small bowel walls, and clearance of the left lower lobe pulmonary artery embolus. Protein S and protein C activity was also requested indicating normal ranges (113.5 and 114.5% respectively). Currently, she is on a regular follow-up at the physician and nephrologist clinic in stable condition and remission of the disease.

DISCUSSION

The heterogeneity of SLE underscores the critical need for a skilled clinician who can effectively discern its diverse clinical manifestations, particularly in the context of corroborative serological findings. Due to these challenges, certain clinicians refer to aspects of the classification criteria when making the diagnosis. According to the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria, a patient can be diagnosed as having SLE if there is an entry criterion (positive ANA ≥1:80) and a score of 10 or more *(Table 2)*. Patients who do not fulfil the classification criteria may still be diagnosed with the disorder[3]. There are several factors that increases the thrombotic risk in SLE patients. The most common risk is the presence of antiphospholipid antibodies which was negative

in this case giving relevance to other pro-thrombotic mechanisms. Firstly, inflammation may affect several steps in blood coagulation: initiation, propagation, and regulation. Secondly, it reduces the fibrinolytic activity and anticoagulant effect of protein C and S. The protein C pathway is one of the most important anticoagulant systems[4]. Such an occurrence denotes that UEDVT may still occur in the absence of APS. UEDVT is an uncommon form of DVT when compared with lower extremity DVT, only accounting for about 4-10% of all DVT cases. Then annual incidence of UEDVT is about 1-2 per 100,000 persons[5]. Although it is important to note that it is becoming increasingly more common secondary to the increased advances in/use of intravascular devices[6]. In the leg gravity affects blood flow and increases stasis, which can lead to clot formation. Lower extremity DVT is more related to factors such as immobility, obesity, trauma, or surgery, where the legs are not very mobile. Whereas UEDVT, is often seen in patients with a central venous catheter, pacemaker leads, or repeated trauma. Because of the high incidence of VTE events in the Seychelles, clinicians maintain a high level of suspicion throughout their shifts, and this resulted in timely diagnosis of UEDVT upon reviewing our patient in the ED. Acute UEDVT may present with swelling and pain in the affected extremity. In certain cases of partial occlusion, the pain and swelling may be minimal and misattributed to superimposed lupus-related joint pains or vasculitis (leading to inflammation and swelling in the limb). In such cases clinicians may fail to consider UEDVT leading to weeks or months of delay. Doppler ultrasound is the initial choice when investigating UEDVT in the ED. The gold standard for diagnosing UEDVT is a CT scan with contrast. Ultrasound is more operator dependent and UEDVT may be missed. It is also not a good imaging test for proximal subclavian or innominate veins due to acoustic shadows from the surrounding bones[7]. Therefore, the absence of VTE in more distal vessels or a negative Doppler ultrasound does not rule out the possibility of UEDVT. The clinician must be careful not to readily overlook this possibility. Especially considering that the incidence of thrombosis in the upper extremity is most common in the subclavian vein (18-67%), followed by the axillary vein (5-25%) and the brachial vein (4-11%), with a marked predilection for the left side[8]. As we can see in this case, the CT scan showed that the thrombus was present in the left axillary, subclavian and brachiocephalic veins. Whereas the Doppler ultrasound was only able to visualize the thrombus within the brachial and basilic veins. Other advantages of contrast-enhanced CT scan are that it can detect thoracic outlet abnormalities or compression or propagation of DVT causing pulmonary embolism, as in our case. Fortunately, the presence of thrombosis within more distal vessels led to the diagnosis of UEDVT. An important consideration is that, once an UEDVT is diagnosed, the clinician must differentiate between primary and secondary UEDVT to guide appropriate management and treatment. The aim of treatment in such cases would be to dissolve the thrombus, alleviate the symptoms, and prevent complications such as pulmonary embolism from occurring. In this case of UEDVT, a repeat CT scan performed 4 months post-treatment revealed complete resolution of thrombosis, including a full therapeutic response.

This case demonstrates that, despite the absence of specific guidelines for UEDVT - particularly in patients with SLE - adapting general DVT management guidelines is effective in achieving a favourable outcome. *(Fig. 5)* However, this may lead to some variability in management amongst physicians worldwide. Early therapy is crucial to prevent subsequent decreases in kidney function. A single episode of lupus nephritis (LN) can lead to irreversible nephron loss, and every subsequent LN flare contributes to organ damage. Prompt diagnosis after onset is associated with better outcomes, regardless of histologic subclass[9]. After being diagnosed with UEDVT and SLE the patient was closely monitored. Therefore, on her follow up appointment it was noted that she had bilateral lower extremity swelling, worsening renal functions and proteinuria. This suggested a rapid onset of LN and was promptly referred to the nephrologist for further management. LN in itself becomes a further contributor to the high thrombotic risk. Initial therapy involves the administration of anti-inflammatory and immunosuppressive drugs to achieve clinical and immunologic renal response that will prevent progressive nephron loss. Corticosteroid therapy should be instituted if the patient has clinically significant renal disease. Immunosuppressive agents, particularly cyclophosphamide, azathioprine, or mycophenolate mofetil, should be administered if the patient has aggressive proliferative renal lesions[10]. All patients with SLE, regardless of the degree and type of disease activity, should receive treatment with hydroxychloroquine unless contraindicated. It has the added benefit of reducing kidney damage due to LN[10]. Other benefits include reduction in flare rates (including LN flares), higher response to therapy, lower incidence of cardiovascular and thrombotic events. Due to our patient's bleeding risk kidney biopsy was not performed. A good rule when considering a kidney biopsy is if the findings will potentially alter patient management. The patient had an optimal therapeutic response, further supporting the risk-benefit decision to avoid kidney biopsy. Findings from a thorough clinical and laboratory evaluation can be used to predict the histologic type of LN in approximately 70-80% of patients[10]. Clinically in LN class III there is arterial hypertension, and the proteinuria is usually greater than 1 g/day. This patient was exhibiting features suggestive of this class of LN which requires prompt and effective therapy[11].

In conclusion, this case illustrates the prompt diagnosis of SLE upon presenting with UEDVT. In the absence of specific guidelines addressing UEDVT in SLE patients, utilizing general DVT protocols serves as a pragmatic approach. Ongoing documentation and case analysis may reveal further clinical considerations unique to UEDVT in the context of SLE, ultimately contributing to the development of more tailored guidelines for managing these patients in the future.

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