CASE REPORT

# Cutaneous thrombosis in pregnancy: A case report

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## SUMMARY

**Antiphospholipid syndrome (APS) is a multisystem, autoimmune disease, which is characterized by thrombosis which may lead to obstetric complications such as uteroplacental insufficiency and pregnancy loss. Antiphospholipid antibodies promote activation of endothelial cells, monocytes, and platelets, causing an overproduction of tissue factor and thromboxane A2. These factors, together with the typical changes in the hemostatic system during normal pregnancy, result in a hypercoagulable state which is responsible for the thrombosis that is presumed to provoke pregnancy complications associated with APS. Obstetric care is based on combined medical-obstetric high-risk management and treatment with antithrombotic agents. We here report a case of APS involving a 23-year-old presented at 24 weeks of her third pregnancy. She had a history of oligohydramnios and an ectopic pregnancy. She had progressive cutaneous thrombosis at 24 weeks of gestation and oligohydramnios at term. She was prescribed enoxaparin and aspirin. She delivered a healthy baby boy without any postnatal complications. Both the enoxaparin and aspirin were continued up to six weeks postpartum. Her lupus anticoagulant antibody was tested positive.**

## INTRODUCTION

Thrombosis in pregnancy is a major cause of peripartum morbidity and mortality. Data suggests that at least 50% of cases of venous thromboembolism in pregnant women are associated with thrombophilias.[1] Antiphospholipid syndrome (APS) is the most frequent treatable cause of recurrent pregnancy loss. Recurrent miscarriages occurred in 26.4% of women with APS.[2] In another larger cohort, preeclampsia, premature birth, or fetal loss are seen in 10–20% of pregnancies with APS.[3]

Diagnosing and managing patients with APS is a challenge for most clinicians. Here, we report a case of APS who presented with cutaneous thrombosis and oligohydramnios in pregnancy.

## CASE REPORT

A 23-year-old female, G3P1+1 was hospitalised at 24 weeks of gestation for a one-week history of painful bullae which ulcerated on her right 2nd, 3rd, 4th, and 5th toes. Her firstborn, a girl, was delivered via emergency lower segment caesarean section (EMLSCS) for failed induction of labour at 37 weeks of gestation, which was complicated by oligohydramnios and reduced fetal movement. The birth weight was 3.0kg. The cause of oligohydramnios was not established. Her postnatal period was uneventful. Her second pregnancy was a tubal ectopic pregnancy, which was managed by laparoscopic removal of the product of conception.There was no family history of any blood coagulation disorders or autoimmune diseases.

On examination, her vital signs were normal. She had a gravid uterus of 24 weeks size. Her pulse rate was regular. All the peripheral pulses were palpable and equal. There were multiple haemorrhagic bullae on her right foot affecting the dorsal aspect of 2$^{nd}$ to 5$^{th}$ toes (Figure 1a and 1c).The capillary refill time was normal. The calves were not swollen or tender. Examination of the cardiovascular, respiratory, and neurological systems was normal. There were no clinical features to suggest systemic lupus erythematosus (SLE) or other connective tissue diseases. During the hospitalisation, she developed more areas of painful non-blanchable reticulated purpuric macules and patches on distal aspects of both legs, which then became superficially ulcerated.

The differential diagnoses that were considered included cutaneous thrombosis and cutaneous vasculitis. The possible underlying causes such as APS, various inherited or acquired thrombophilia disorders, and SLE were investigated.

A full blood count, renal, and liver function tests, coagulation screen, urinalysis,and immunologic profile including antinuclear antibody (ANA), C3, and C4 were also normal. Hepatitis viral screening, p- and c-antineutrophil cytoplasmic antibody (ANCA) did not reveal any abnormalities. Lupus anticoagulant (LA), anti-cardiolipin antibodies (ACL), and anti–β-2-glycoprotein I (aß2GPI) for IgG were not detected in her thrombophilia screen at 24 weeks of gestation. Doppler ultrasound showed no sonography evidence of right lower limb deep vein thrombosis. Echocardiogram and uterine artery doppler at 24 weeks were normal.

A skin biopsy of a purpuric patch on the right calf showed normal epidermis within travascular thrombi inall small and medium vessels of dermis and hypodermis, associated with haemorrhage and minimal inflammatory cells(Figure 2a–c). Immunofluorescence study showed no depositions of IgG, IgM, C3, and C1 around the vessels or at the dermo-epidermal junction. She was confirmed to have cutaneous thrombosis.

Low molecular weight heparin (LMWH) of subcutaneous enoxaparin 80mg twice a day and oral aspirin 150mg daily

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**Table I: Vasculopathy in antiphospholipid syndrome: summary of vascular involvement.(Adapted from Sal,a S et al..[4])**

| Organ | Clinical manifestation | Vascular pathology |
|---|---|---|
| Brain | Multi-infarct dementia, seizures | Endothelial proliferation |
| Coronary artery | Valve abnormalities (valve thickening and vegetations), occlusive arterial disease (atherosclerosis and myocardial infarction), intracardiac emboli, ventricular dysfunction | Endothelial proliferation |
| Lung | Pulmonary hypertension | Plexiform lesions (i.e. endothelial proliferation) |
| Renal artery | Hypertension | Smooth muscle cells |
| Intrarenal vessels | APS nephropathy | Endothelial and smooth muscle cells proliferations |
| Placenta | Placenta-mediated complications | Decidual vasculopathy (i.e. endothelial proliferation) |
| Peripheral artery | Peripheral artery disease, critical ischaemia | Endothelial and smooth muscle cells proliferations |
| Skin | Livedo, livedoid vasculopathy | Endothelial proliferation |

**Table II: Classification criteria for definitive antiphospholipid syndrome (adapted from the revised Sapporo classification criteria[12]).**

| | |
|---|---|
| Vascular thrombosis | ≥ 1 clinical episode of arterial, venous or small vessel thrombosis. Thrombosis must be objectively confirmed. For histopathological confirmation, thrombosis must be present without inflammation of the vessel wall. |
| Pregnancy morbidity | 1. ≥1 unexplained death of a morphologically normal fetus ≤ 10 weeks gestation.<br>2. ≥1 premature delivery of a morphologically normal fetus <34 weeks gestation because of:<br>• severe preeclampsia or eclampsia defined according to standard definition<br>• recognized features of placental insufficiency*<br>3. ≥ 3 unexplained consecutive miscarriages <10 weeks gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded. |
| Laboratory criteria to | The presence of APLA, on two or more occasions at least 12 weeks apart and no more than 5 years prior clinical manifestations, as demonstrated by ≥1 of the following:<br>1. Presence of lupus anticoagulant in plasma.<br>2. Medium to high-titer anticardiolipin antibodies (>40GPL or MPL, or >99th percentile) of IgG or IgM isoforms.<br>3. Anti-β2 glycoprotein-I antibody (anti-β2GP I) of IgG or IgM present in plasma. |

APS, antiphospholipid syndrome; APLA, antiphospholipid antibodies; GPL, grams per liter: MPL, micrograms per liter.
* Features of placental insufficiency include abnormally thin placenta (less than 1 cm), circumvallate placenta (1% of normal placentas), amnion cell metaplasia, amnion nodosum, increased syncytial knots, calcifications, infarcts due to focal or diffuse thickening of blood vessels, villi capillaries occupying about 50% of the villi volume or when <40% of capillaries are on the villous periphery. Placental insufficiency can lead to intrauterine growth retardation, oligohydramnios, fetal heart rate abnormalities indicating fetal hypoxia and eventually fetal death.
The classification criteria for definitive antiphospholipid syndrome requires that a patient fulfills the laboratory and clinical criteria. As outlined previously, the laboratory criteria include the presence of persistent antiphospholipid antibodies, whereas the clinical criteria include manifestations such as thrombosis and/or pregnancy morbidity.

was initiated. The initial necrosis on the lower limbs gradually improved (Figure 1b and 1d) while she developed new reticular purpuric patches on her right elbow, left thigh, and bilateral shins. In addition, focal areas of painful ulceration and necrosis developed on the purpuric patches. Compliance to medications was reinforced repeatedly to the patient. These lesions improved albeit slowly with the continuation of both enoxaparin and aspirin at the same dose.

She was under close follow-up by a team comprised of materno-fetal obstetrician and haematologist. The fetal growth was according to gestation. However, towards the end of pregnancy, she had oligohydramnios without history of leaking liquor. A healthy baby boy weighing 3.8kg was delivered via EMLSCS at 39 weeks of gestation. Postnatally, there was a rapid resolution of her skin lesions. She continued the subcutaneous enoxaparin and aspirin until 6 weeks postpartum without any bleeding complications. An intrauterine contraceptive device was inserted as a contraceptive measure.

Her thrombophilia screening was repeated 4 months after the anticoagulant and antiplatelet were discontinued. Her LA was positive. ACL and aß2GP1 were not detectable. Protein C, protein S, and antithrombin activity levels were within normal ranges. Her LA was however undetected on repeated test at 10 months post anticoagulant therapy. She was finally diagnosed to have APS. She was planned to re-initiate LMWH from fetus viability until 6 weeks postpartum in future pregnancies.

## DISCUSSION

APS is the most important acquired autoantibody-mediated thrombophilia. It is a systemic condition affecting multiple organs as shown in Table I.[4] In a study of 200 patients with APS, dermatologic manifestations were observed in 49%.[5] Cutaneous manifestations were the initial presenting complains in about a third of them.There are myriad of dermatological manifestations in APS. The most commonly documented rash associated with APS syndrome was livedo reticularis, which typically affects the lower limbs. Other

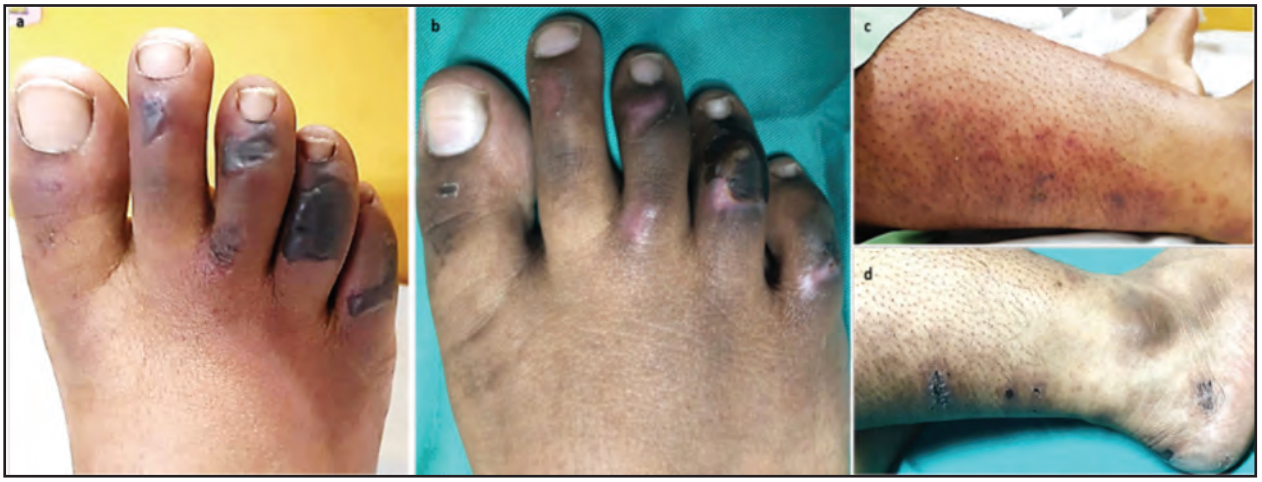


**Fig. 1:** (a, c)Multiple haemorrhagic bullae on toes and non-blanchable purpuric patches on calves at first presentation;(b, d)Healing ulcers on toes with porcelain white, atrophic, stellate scars (atrophie blanche), reduced swelling, resolved reticular purpuric patches and netlike pattern of hyperpigmentation seen on the calf on follow-up at 28 weeks of gestation

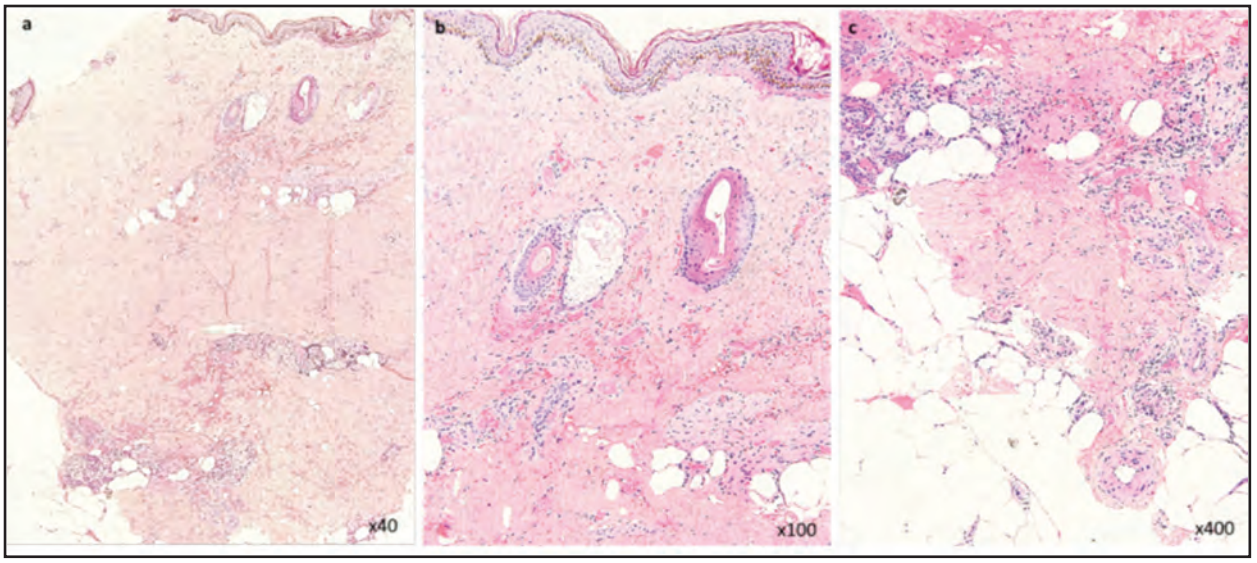


**Fig. 2:** (a-c) Histopathology of skin biopsy stained with hematoxylin and eosin showed the presence of subepidermal fibrin collection. The superficial dermis exhibits scattered neutrophilic infiltration, nuclear ducts, and extravasated red blood cells. There are numerous thrombosed blood vessels in the superficial dermis extending to deep dermis and hypodermis

dermatological manifestations of APS are skin ulcerations, digital gangrene, superficial venous thrombosis, pseudovasculitis lesions, purpura, palmar or plantar erythema, nodules, pustules, malignant atrophic papulosis-like lesions, superficial skin necrosis, superficial phlebitis, multiple subungual splinter haemorrhages, primary anetoderma, extensive cutaneous necrosis, and white-atrophy-like lesions.[6]

Adverse pregnancy outcomes in APS include recurrent early abortions, fetal death, intrauterine growth restrictions, premature birth due to preeclampsia, and other placenta-mediated complications. These conditions result in fetal hypoxia, an indicator of uteroplacental insufficiency. Our patient had oligohydramnios in both her pregnancies. The first pregnancy was an early term delivery. There was fetal distress as evidenced by reduced fetal movement. This could reflect uteroplacental insufficiency, suggesting that spiral artery vasculopathy may be the contributary factor. Regrettably, the placenta of her both pregnancies was not examined histologically after delivery.

Besides skin and obstetric manifestation, APS is a major risk factor for arterial thrombotic events such as ischaemic stroke and myocardial infarction.[4] Rarely, catastrophic antiphospholipid syndrome (CAPS), also known as Asherson's syndrome may occur. It is characterized by multiorgan failure due to multiple small vessel thrombosis associated with thrombotic microangiopathy. It occurs in less than 1% of APS.[3] CAPS was triggered by an identifiable factor mainly infections, trauma or surgery, anticoagulation withdrawal, malignancies, lupus flares, and/or pregnancy in

50% of patients. In pregnancy, CAPS usually follows HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome, which can be associated with preeclampsia or eclampsia. Close monitoring of patient's full blood count, liver function test, and blood pressure is vital in the management of such patients.

Testing for APLA should be considered in recurrent pregnancy loss or stillbirth. In the original 1999 Sapporo classification, the diagnosis of APS is established when the APLA is present together with any of these three clinical criteria: (1) three or more consecutive unexplained miscarriages before the 10th week of gestation, (2) one or more unexplained death of a morphologically normal fetus at 10 weeks of gestation or later, or (3) one or more premature births of a morphologically normal fetus at 34 weeks of gestation or earlier, associated with severe pre-eclampsia or placental insufficiency.[7] As illustrated in Table II, the revised Sapporo classification (The Sydney criteria), were proposed in 2006 for the classification of true APS. In this revised classification, the clinical criteria remained unchanged, but the laboratory criteria were revised. IgG or IgM anti-β 2GPI antibody test were added to the laboratory criteria. In addition, the follow-up interval was prolonged from 6 weeks to 12 weeks.

Our patient initially tested negative for LA. A normal coagulation factor or inhibitors test results in the acute setting of thrombosis should be interpreted with caution. Aboud et al. proved that testing at the time of a thrombotic event may result in 'false-negative' LA result.[8] Testing is more accurate once the prothrombogenic mechanism is arrested and acute phase reactants lowered. Thus, the best time for an accurate assessment of thrombophilia is at least six months after an acute thromboembolic episode and at least four to six weeks after stopping antithrombotic therapy. Testing should be repeated at least 12 weeks apart, and the diagnosis of thrombophilia is confirmed if at least two or more subsequent test results are positive.

APLA fluctuates over time. Our patient was retested at 4 months and 10 months after completing her anticoagulant treatment. The test showed positive LA initially but was undetected at 10 months post anticoagulant. Loss of positivity of APLA post-thrombosis has been observed in clinical practice, especially those with secondary APS. If it occurred just at the time of thrombosis, it might reflect loss due to deposition in the thrombosis. This shows how difficult it is to define a patient as 'positive' or 'negative' for the APL markers, given the fluctuations over time, and high false-negative and false-positive rates for LA detection.[8] Thus, an overall interpretation of all LA testing, combined with the patient's clinical information is required to make an appropriate diagnosis. Therefore, patients with thrombotic events need to be treated with anticoagulants immediately although the cause of thrombosis may or may not be confirmed later.

The current recomended treatment of thrombotic and obstetric APS is antithrombotic agents. The anticoagulant of choice during pregnancy is LMWH, although adjusted-dose unfractionated heparin (UHF) can also be used. Warfarin is usually avoided after the first trimester because of concern for warfarin embryopathy. Anticoagulation should be continued throughout delivery and for six weeks postpartum In the postpartum period, either continuation of LMWH or bridging to warfarin with the aim to achieve a therapeutic International Normalized Ratio (INR) of 2 to 3 are acceptable options. The combination of aspirin and LMWH has resulted in a live-birth rate of over 70%.[9]

Our patient was started on LMWH and was continued until 6 weeks postpartum. Low-dose aspirin was also prescribed to reduce the theoretic potential for adverse effects on the placental microcirculation. Both aspirin and LMWH are safe for the fetus in pregnancy. For future pregnancies, patients with previous thrombosismay be put on long-term anticoagulants prior to conception.

Pregnancy outcome is optimized when pregnancy is planned in patients with APS. Patients are generally advised to use contraception to avoid pregnancy if they have severe disease-related damage, during active disease and while on teratogenic medications such as warfarin.[10] Given the additive effects of multiple risk factors, combined hormonal contraceptives are not advised for use in APS patients.[10] Progesterone-only contraceptives likely represent the best option for APS patients, as there is little-to-no demonstrated an increased risk for thrombosis.[10] The risks and benefits of each method need to be explained to patients with APS in the childbearing age.[10]

## CONCLUSION

In summary, we described a young mother who presented with cutaneous thrombosis at the end of second trimester of pregnancy with recurrent oligohydramnios, whom later confirmed to have APS. The use of LMWH in combination of aspirin has resulted a favourable maternal and fetal outcome in our patient. This case highlights the importance of a skin biopsy of the skin lesions which allowed early diagnosis of thrombosis when thrombophilia screening during pregnancy and active thrombotic event is usually false negative. Initiation of appropriate antithrombotic treatment will improve the pregnancy outcome and prevent potential complications of the disease.

## CONFLICT OF INTEREST

None

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