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CASE REPORT

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Primary antiphospholipid syndrome in a male presents with acute digital ischemia: Dramatic response to glucocorticoid

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Key Clinical Message

We present a rare case of primary antiphospholipid syndrome in a 38-year-old male who presented with painful digital ischemia. Early initiation of anticoagulation and addition of glucocorticoid led to a significant improvement in the patient.

KEYWORDS

acute digital ischemia, antiphospholipid syndrome, glucocorticoid, lupus anticoagulant, male, thrombosis

1 | INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies, namely, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or antibodies to the protein cofactor-β_2 glycoprotein I (anti-β_2GPI) which cause a hypercoagulable state resulting in recurrent venous, arterial or small vessel thromboembolism and/or pregnancy-related complications.[1–3] Thrombus can be either venous (59%) or arterial (28%) or both arterial and venous (13%).[2] It was first described by Hughes in 1983, hence also known as Hughes syndrome.[4] In 1992, another subset of APS (<1%), termed catastrophic APS, was identified where multiple small vessels supplying major organs infarct within a short period of time leading to multi-organ failure and high mortality (>50%).[5–7] APS is far more prevalent in women than men in the adult age group (5:1), and only 1.9% of patients present with digital ischemia and gangrene at disease onset.[6] High clinical suspicion of this potentially life-threatening condition and early initiation of management will prevent morbidity and mortality associated with primary APS. This paper reports a rare case of primary APS in a young male who presented with acute digital ischemia and was successfully treated with a combination of anticoagulation and glucocorticoid.

2 | CASE HISTORY/EXAMINATION

A 38-year-old male with no remarkable past medical history was admitted to our inpatient medicine department with complaints of sudden severe pain in all fingers and toes for 2 days and blackening of the tip of the right middle finger for 1 day.

He had no history of fever, cough, weight loss, anorexia, hearing abnormality, abdominal pain, epistaxis, or bleeding from any site of the body. He also did not have any history of oral or genital ulcer, rash, photosensitivity,

alopecia, paresthesia, or limb weakness. To note, he was normotensive, non-diabetic, and a heavy smoker with a 24-pack-year smoking history. He is a businessman residing in an urban area. His family history was unremarkable for APS, hypercoagulable state, or any other autoimmune disease.

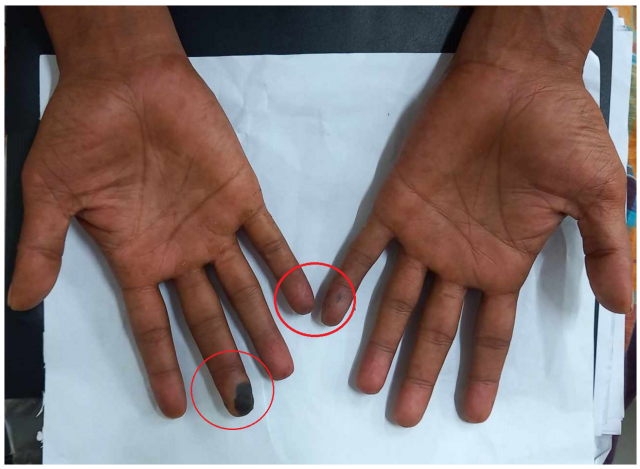

FIGURE 1 Figure showing black discoloration and necrosis of the finger pulp of the 3rd digit of the right hand and ischemic changes of the 5th digit of both hands.

On clinical examination, the patient was conscious, oriented, and hemodynamically stable. All peripheral pulses were symmetrically present. All systemic examinations were normal except for nail infarction with a tender and necrosed finger pulp of 3rd digit of the right hand and ischemic changes of 5th digit of both hands (Figure 1).

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATION AND TREATMENT

Investigations revealed normocytic normochromic anemia with mild thrombocytopenia, high erythrocyte sedimentation rate (ESR), and elevated C-reactive protein. Urinalysis showed trace albuminuria. Random blood sugar, serum creatinine, electrolytes, electrocardiogram, echocardiogram, ultrasonography of the abdomen, and chest x-ray were normal. Activated partial thromboplastin

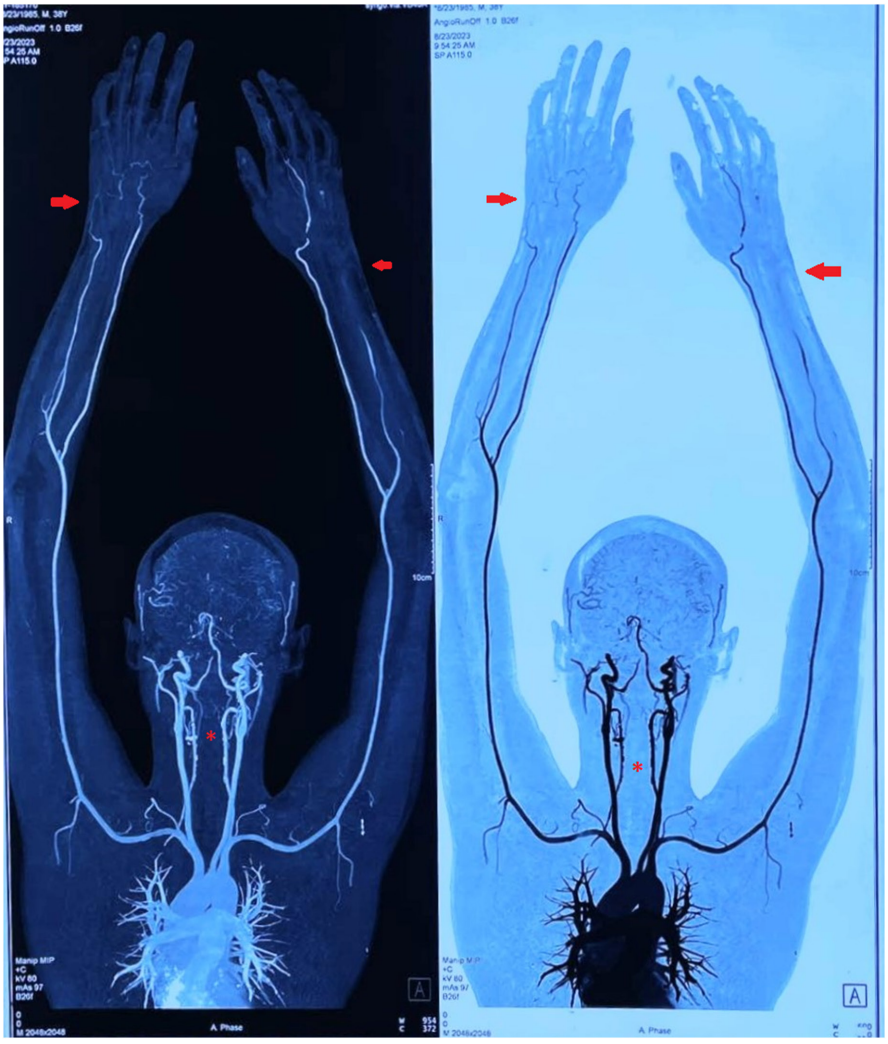

FIGURE 2 CT angiogram of both upper limbs showing slightly thin flow in the right ulnar and interosseous artery, mild diffuse narrowing in the right vertebral artery, and significant thin distal flow in the left ulnar and interosseous artery.

time (aPTT) was elevated. Antinuclear antibody (ANA), anti-double-stranded DNA (Anti-dsDNA), cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), extractable nuclear antigen (ENA) profiles were also normal. CT angiogram of both upper and lower limbs showed narrowing with a thin flow of multiple distal arteries (Figures 2 and 3).

Based on his acute digital ischemia and a prolonged aPTT, a diagnosis of acute digital ischemia secondary to primary APS was suspected. Later, specific antibody testing for APS was positive for LA. We also excluded other causes of hypercoagulability (Table 1).

After consultation with the Department of Vascular Surgery and Rheumatology, a diagnosis of primary APS was made. Immediate anticoagulation with low molecular weight heparin, and high-intensity statin was started.

However, after 4 days of treatment, there was no significant improvement in the patient's symptoms. At that point, we decided to start pulsed methylprednisolone 1 g intravenously. On the 2nd day of methylprednisolone treatment, there was a significant improvement in the patient's pain in the fingers, complete resolution of digital ischemia of the 5th digit of both hands and a moderate improvement in the tenderness in the finger pulp of the 3rd digit of the right hand. After 5 days, we discharged the patient with warfarin plus low-dose aspirin (target INR 2–3), high-intensity statin, and tapering dose of steroid (prednisolone 60 mg tapered over 2 months).

4 | OUTCOME AND FOLLOW-UP

After 3 months of follow-up, our patient did not experience any new symptoms with an INR of 2.4 (Figure 4) ESR and C-reactive protein return to normal levels. The follow-up CT angiogram of both upper and lower limbs was normal. The LA test was still positive, which confirmed our initial diagnosis of primary APS. The patient is currently under regular follow-up every 3 months with no new episode of thromboembolic event reported to date.

5 | DISCUSSION

APS can be either primary or secondary due to any other condition. Approximately 53% of cases are primary while around 36% of cases are secondary to systemic lupus

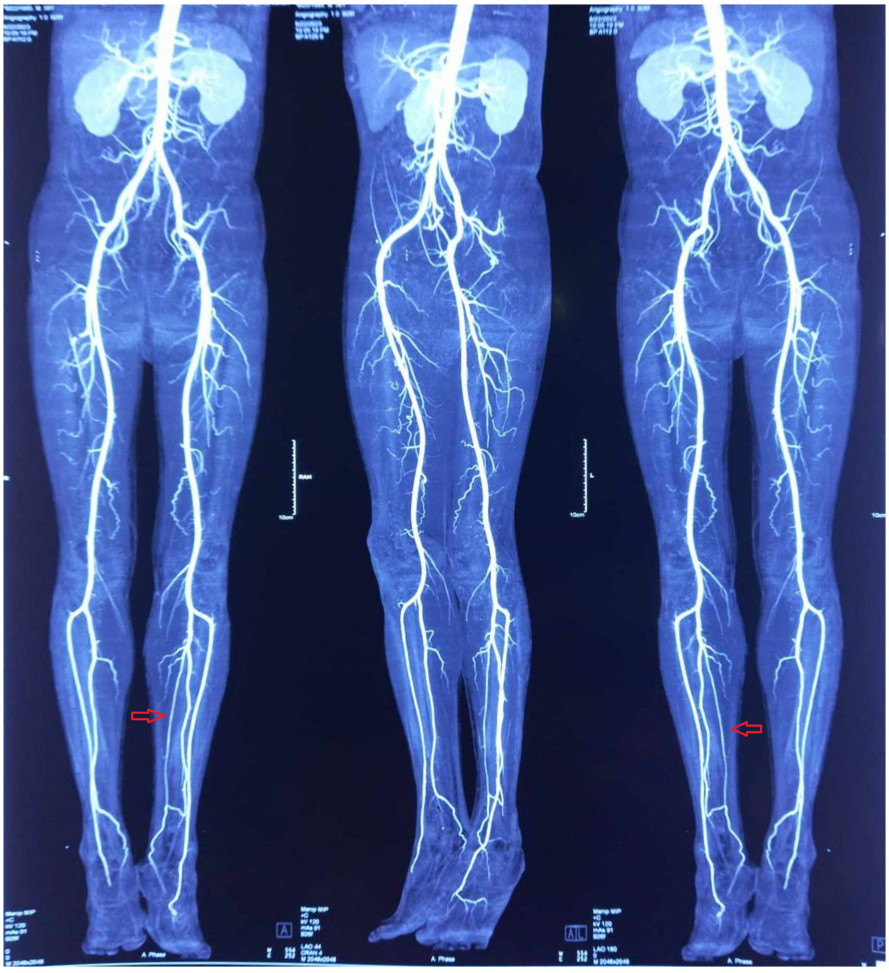

FIGURE 3 CT angiogram of the abdominal aorta and both lower limbs showing narrowing with significant thin flow in the right posterior tibial artery and moderate diffuse narrowing in the left posterior tibial artery.

TABLE 1 Comprehensive overview of all relevant investigations conducted on our patient.

Test	Result	Reference
Hemoglobin	126 g/L	140–180 g/L in male
HCT	40.20%	42%–50% in male
WBC	11.80×10^9/L	$4.5–11 \times 10^9$/L
Neutrophil	70%	40%–70%
Lymphocyte	23%	20%–45%
Monocyte	5%	2%–8%
Eosinophil	2%	1%–4%
Basophil	0%	0%–1%
Platelets	115×10^9/L	$150–450 \times 10^9$/L
Peripheral blood film	Normocytic normochromic anemia with mild thrombocytopenia	
Serum creatinine	97.24 μmol/L	62–115 μmol/L
ESR	97 mm in 1st hour	0–12 mm in 1st hour
C-Reactive protein	107 mg/L	<5.00 mg/L
Urine analysis	Albumin: trace	
Total cholesterol	5.02 mmol/L	<5.17 mmol/L
HDL-cholesterol	1.03 mmol/L	<1.03 mmol/L
LDL-cholesterol	3.49 mmol/L	<2.59 mmol/L
Triglycerides	1.73 mmol/L	<1.69 mmol/L
Random blood sugar	6.1 mmol/L	<7.8 mmol/L
HBsAg	Negative	
Anti HCV	Negative	
S. TSH	2.25 milliunits/L	0.5–4 milliunits/L
Anti-nuclear Ab (ANA)	0.20 kIU/L	>1.20 kIU/L: Positive 1.0–1.2 kIU/L: Equivocal < 1.0 kIU/L: Negative
Anti-ds DNA	5.80 kIU/L	<20 kIU/L: Negative 20–25 kIU/L: Equivocal >25 kIU/L: Positive
C-ANCA	1.20 kIU/L	Normal: <5 kIU/L Elevated: >5 kIU/L
P-ANCA	0.60 kIU/L	Normal: <5 kIU/L Elevated: >5 kIU/L
Anti-RNP antibody (IgG)	2.70 kIU/L	Normal: <15 kIU/L Borderline: 15–25 kIU/L Elevated: >25 kIU/L
Anti-Smith antibody (IgG)	0.70 kIU/L	Normal: <15 kIU/L Borderline: 15–25 kIU/L Elevated: >25 kIU/L
Anti-SSA/Ro Antibody (IgG)	1.30 kIU/L	Normal: <15 kIU/L Borderline: 15–25 kIU/L Elevated: >25 kIU/L
Anti-SSB/La antibody (IgG)	1.90 kIU/L	Normal: <15 kIU/L Borderline: 15–25 kIU/L Elevated: >25 kIU/L

TABLE 1 (Continued)

Test	Result	Reference
Anti-ScL-70 antibody (IgG)	1.80 kIU/L	Normal: <15 kIU/L Borderline: 15–25 kIU/L Elevated: >25 kIU/L
Anti-Jo-1 antibody (IgG)	1.00 kIU/L	Normal: <15 kIU/L Borderline: 15–25 kIU/L Elevated: >25 kIU/L
Anti-beta-2-glycoprotein-I antibodies (anti-β2GPI)	5.30 MPL units	Negative: 0–10 MPL units Positive: >10.0 MPL units
Anticardiolipin Ab (aCL)	3.60 MPL units	Normal: <10 MPL units Elevated: >10 MPL units
Lupus anticoagulant 1 (LA1)	74.20 s	31–44 s
Lupus anticoagulant 2 (LA2)	40.50 s	30–38 s
Lupus ratio (LR)	1.83	>2: Strongly present 1.5–2: Moderately present 1.2–1.5: weakly present
Activated partial thromboplastin time (aPTT)	78.50 s	30–40 s
Protein C activity	82.50%	65%–135%
Protein S activity	76.35%	60%–113%
Antithrombin III activity	90.10%	80%–120%

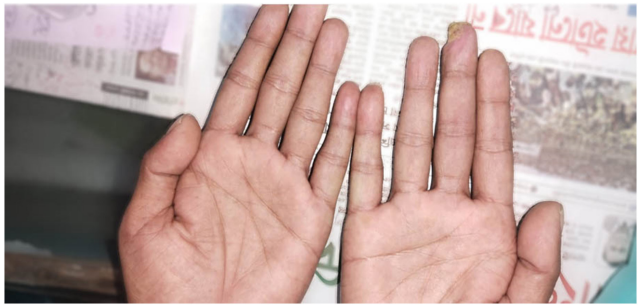

FIGURE 4 At 3 months of follow-up, figure of the hands showing complete resolution of digital ischemia with healed necrosis of the 3rd digit of the right hand.

erythematosus. Other causes leading to APS are Sjogren's syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitis, dermatomyositis, etc.[6,8] Rates of pregnancy loss, arterial and venous thrombosis are similar in both primary and secondary APS.[8]

APS can present a wide range of clinical features. The most common clinical feature is deep vein thrombosis (38.9%). Other common manifestations are migraine (20.2%), stroke (19.8%), livedo reticularis (24.1%), arthralgia (38.7%), pulmonary embolism (14.1%), valve dysfunction (11.6%), while around 35.4% patients present with early (<10 weeks) fetal losses.[6]

Although around 50% of patients present with various dermatological symptoms, 3.3%–7.5% of APS patients develop digital gangrene, while it is the presenting feature among only 1.9%–2.5% of individuals.[2,6,7,9] Risk factors for thrombotic events such as smoking, hypertension, oral contraceptive pills, dyslipidemia, infection, immobilization, trauma, and surgery may contribute to gangrene development.[2,10,11] Our patient was a smoker, which is a risk factor. Gangrene can be preceded by distal erythema, cyanotic macules, or pseudo-cellulitis resulting in necrosis and occasionally leading to amputation of the digits.[7,9] Peripheral pulses may be preserved or absent.[2] Angiography may show large or medium size vessel stenosis.[9] CT Angiogram of our patient showed narrowing of multiple distal arteries and thinning of distal flow.

The revised Sapporo criteria (2006) is commonly used to diagnose APS. This requires at least one clinical criteria (vascular thrombosis or pregnancy-related morbidity) as well as at least one antiphospholipid antibody (LA/aCL/anti-β_2GPI) being present in the blood on two or more occasions at least 12 weeks apart.[12] 2023 ACR/EULAR criteria have adopted a scoring system within clinical and laboratory domains for the classification of APS.[13]

Our patient had digital gangrene along with positive LA. As this was his initial presentation, a repeat LA test was done again after 12 weeks. The persistence of the LA test 12 weeks later confirmed our initial diagnosis of APS

according to the revised Sapporo criteria.[12] Again, according to 2023 ACR/EULAR criteria, APS was confirmed as he had arterial thrombosis without a high-risk CVD profile as well as thrombocytopenia. His score was 6 in the clinical domain and 5 in the laboratory domain.[13]

Digital gangrene is a major thrombotic event that requires full anticoagulation with heparin.[1] Initially, when we diagnosed the patient as a case of acute digital ischemia secondary to primary APS, immediate treatment with low molecular weight heparin and high-dose statin was started. As the patient didn't respond to the treatment and his limb was threatened, we added pulsed methylprednisolone 1 gram intravenously daily for 5 days. Although the role of glucocorticoid and other immunosuppressives are debated in such cases and favored more in cases of catastrophic APS, our patient showed a dramatic response to glucocorticoid.[7,8,14,15]

As this was the first arterial presentation of our patient, according to EULAR guidelines, ideal prophylaxis options were warfarin (target INR 2–3), warfarin (target INR 3–4), and warfarin plus low-dose aspirin (target INR 2–3).[16] Long-term prophylaxis should be given due to the risk of high recurrence (69%–91%).[8,17] Considering his initial unresponsiveness to anticoagulation therapy alone, we assessed the bleeding risk of the patient and discharged him with warfarin plus low-dose aspirin (target INR 2–3). High-intensity statin was given as it inhibits tissue factor production induced by anti-phospholipid antibodies in cultured human endothelial cells and decreases the adhesiveness of endothelial cells induced by anti-β2-glycoprotein I.[15,18] The patient was also advised to stop smoking as it is a significant risk factor that may predispose to recurrent thrombotic events.[19]

6 | CONCLUSION

Male patients with signs of acute thromboembolic events without any evidence of vasculitis or autoimmune disease should be evaluated for APS. The patients should be started on anticoagulants immediately. Glucocorticoids may be considered in anticoagulant non-responsive cases.

AUTHOR CONTRIBUTIONS

Tanvir Ahammed: Supervision; writing – original draft. **Mohammad Rasel:** Writing – original draft; writing – review and editing. **Sourav Saha:** Writing – original draft. **Ashif Istiak:** Writing – original draft. **Sabreena Chowdhury:** Writing – original draft.

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CONFLICT OF INTEREST STATEMENT

All the authors of this manuscript have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

Ethics approval is not required for de-identified single case reports based on institutional policies.

CONSENT

Written informed consent was obtained from the patient to publish this case report in accordance with the journal's patient consent policy. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

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