CASE REPORT

Multiple subcutaneous nodules and saccular abdominal aortic aneurysms as the presentations of primary antiphospholipid syndrome

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SUMMARY

Antiphospholipid syndrome (APS) is an acquired multisystem hypercoagulable disorder characterised by arterial and/or venous and/or microvascular thrombosis and/or pregnancy-related complications together with persistently elevated antiphospholipid antibodies (aPL). Here we describe a case of APS in a 46-year-old previously healthy man who presented with a 1-year history of intermittent high fever, multiple painful subcutaneous nodules over both lower limbs and worsening lower abdominal pain. Saccular aneurysms involving the left infrarenal aorta, aortic bifurcation and proximal right common iliac artery were reported in the computed tomography (CT) aortogram. He was initially treated as mycotic aneurysms with erythema nodosum with prolonged antibiotics, without any improvement. Physical examination at presentation revealed ill-defined, tender, purplish papules and nodules on his lower limbs. Investigations revealed normochromic normocytic anaemia (haemoglobin 10.1 g/dL), total white cell count 9.45 × 10^9/L, elevated erythrocyte sedimentation rate (111 mm/hr) and c-reactive protein (92.7 mg/L). Antinuclear antibodies and extensive microbiological studies were negative. Histopathological examination of the subcutaneous nodules showed small and medium vessel thrombosis without vasculitis, and negative direct immunofluorescence stain. Following that, he was found to have positive lupus anticoagulant and immunoglobulin G (IgG) anticardiolipin antibodies. The diagnosis of primary antiphospholipid syndrome was finally made, and warfarin was initiated. His subcutaneous nodules and abdominal aneurysms resolved completely within two months. Here we highlight the importance of skin biopsy in the diagnosis of APS. There should be a high index of suspicion for this rare condition as early diagnosis and treatment lead to better clinical outcomes and may avoid complications such as aneurysms.

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired multisystem hypercoagulable disorder. This condition has variable clinical presentations, and a high index of suspicion is necessary to clinch the diagnosis. We describe a patient with primary APS who presented with subcutaneous nodules and abdominal aortic aneurysms which are unusual presentations of this condition.

CASE PRESENTATION

A 46-year-old Chinese man presented with recurrent painful subcutaneous nodules on his lower limbs for the past 1 year. He sought treatment at a private dermatology clinic 6 months ago. A skin punch biopsy of a left thigh nodule was reported as erythema nodosum. Direct immunofluorescence was negative. He was treated with a course of antibiotic.

A month later, he developed intermittent lower abdominal pain that gradually became persistent and was associated with fever. Upper and lower endoscopy were performed by a private gastroenterologist, and histopathological examination of the colon revealed mild non-specific proctitis. Subsequently, a computed tomography (CT) of the abdomen was performed as his symptoms persisted. CT abdomen revealed aortic aneurysm. A CT aortogram (Figure 1b) demonstrated saccular aneurysms involving the left infrarenal aorta, aortic bifurcation and proximal right common iliac artery. The proximal right common iliac artery aneurysm was associated with perivascular hematoma that caused significant compression and stenosis of the right common iliac artery. He was treated for mycotic aortic aneurysms with IV ceftriaxone 2 g daily for 10 days and underwent endovascular aneurysm repair (EVAR) with right internal iliac artery embolisation (Figure 1c). After surgery, he was commenced on IV amoxicillin/clavulanic acid 1.2 g thrice daily, which was then replaced by the oral route upon discharge.

He was readmitted a week later with fever and painful nodules over his lower limbs (Figure 1a) for 3 days. Further history revealed that he had intermittent oral ulcer that healed spontaneously without scarring for the past 3 months. He denied any joint pain, alopecia, eye symptoms, genital ulcers, headache, weight loss or night sweats. There was no recent history of travel or contact with patients with tuberculosis. Family history was negative for connective tissue disease or cardiovascular diseases. His past medical

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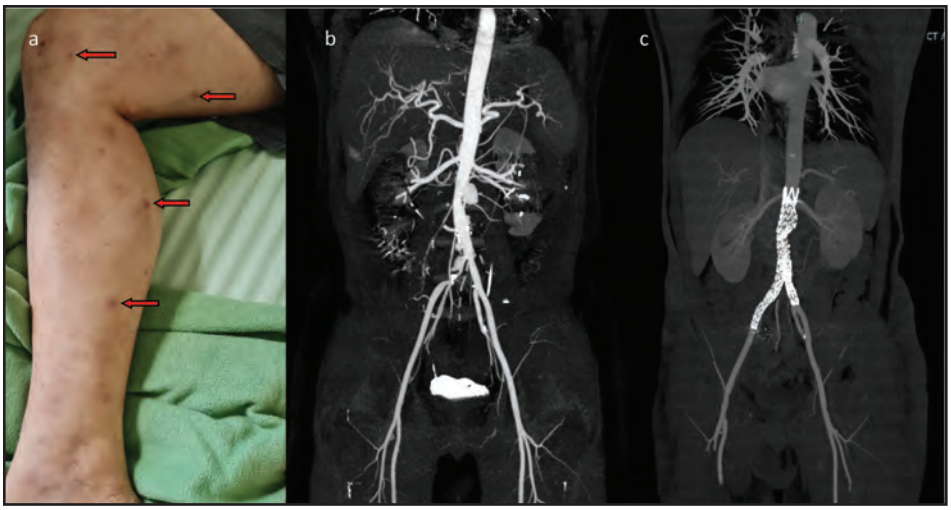

Fig. 1: a) Several discrete, violaceous, tender nodules over the right lower limb. Computed tomography (CT) images showed b) Pre-EVAR (endovascular repair of aortic aneurysm): saccular aneurysms at the left infrarenal aorta, aortic bifurcation, right common iliac artery c) Post-EVAR: EVAR stent *in situ*

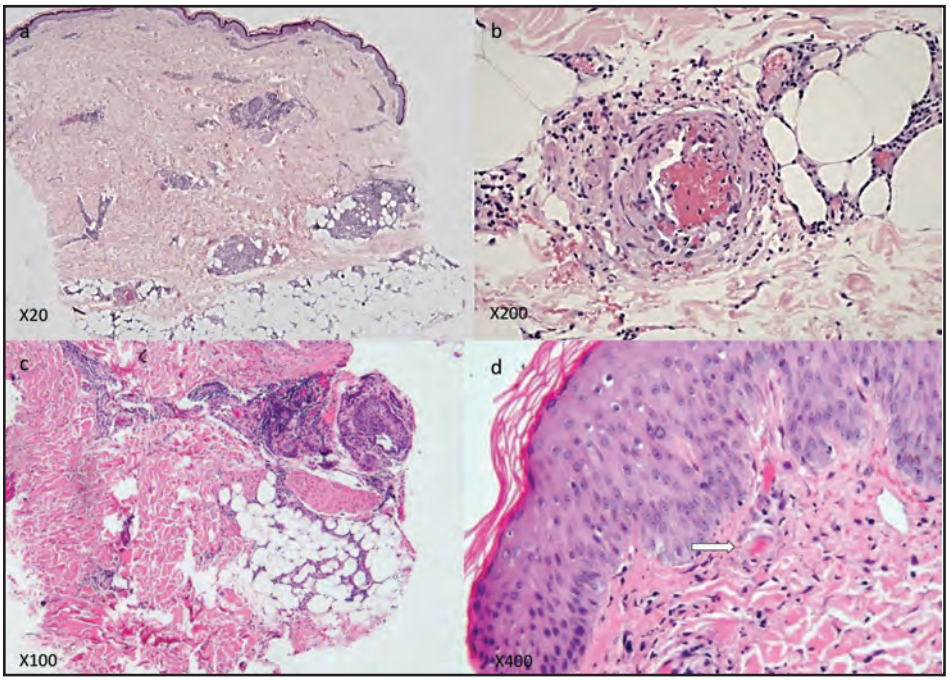

Fig. 2: Histopathological examination of skin biopsy performed at our centre (haematoxylin and eosin) showed a) infiltrates over periadnexal and perivascular areas with vessel thrombosis in the dermis and subcutaneous tissue; b) at higher magnification showed intraluminal fibrin thrombi with extravasated red blood cells and perivascular lymphocytic and histiocytic infiltrates. Histopathological examination of skin biopsy performed at a private centre one year before presenting to us (haematoxylin and eosin) showed c) panniculitis; d) at higher magnification showed vessel thrombosis in the deep dermis

history includes hypertension on oral amlodipine 5 mg daily. He was an active smoker and denied any intravenous or recreational drug use. Physical examination revealed several discrete, purplish, tender papules and nodules on his lower limbs. Examination of the cardiovascular, respiratory and neurological system were normal.

Several differentials were considered including infectious panniculitis, erythema induratum of Bazin, polyarteritis nodosa, Behcet's disease and vasculopathy.

Blood investigations showed normochromic normocytic anaemia (haemoglobin 10.1 g/dL), elevated alanine transaminase (ALT 74 U/L), erythrocyte sedimentation rate (ESR 111 mm/hr) and c-reactive protein (92.7 mg/L). Renal function was normal. Investigations for infective cause were negative for mycoplasma, leptospirosis, hepatitis B, hepatitis C, HIV, cytomegalovirus immunoglobulin M (IgM) and Epstein-Barr virus IgM. Blood cultures and QuantiFERON TB were also negative. Autoimmune screen including rheumatoid factor, antinuclear antibodies and

antineutrophil cytoplasmic antibodies were negative. Hypercoagulable screen was positive for lupus anticoagulant (LAC) and anticardiolipin (aCL) IgG but negative for aCL IgM and β2-glycoprotein I antibodies (anti-β2GPI). A repeated CT aortogram revealed that all previous aneurysms were thrombosed, and EVAR stent was *in situ*.

Histopathological examination of skin biopsy of the right posterior calf nodule showed small and medium vessel thrombosis in the mid-dermis and subcutaneous tissue with no vasculitis (Figure 2a and b). His initial biopsy performed a year ago at a private centre was re-examined with deeper sections which showed small vessel thrombosis with panniculitis in the subcutaneous tissue (Figure 2c and d), similar to our present biopsy. Tissue for bacterial culture, Mycobacterium tuberculosis culture and polymerase chain reaction (PCR), non-tuberculous mycobacterial culture and PCR, fungal culture and PCR were negative.

In view of the skin biopsy findings, positive LAC and aCL IgG and no underlying autoimmune disease, he was diagnosed with primary APS. He was commenced on warfarin and had complete resolution of subcutaneous nodules and abdominal pain. A repeat CT scan at 2 months after warfarin initiation showed resolution of abdominal aneurysms. He was planned to complete warfarin for at least 6 months and to repeat the antiphospholipid antibodies 6 months after discontinuing warfarin.

DISCUSSION

APS is a multisystem prothrombotic disorder with a definitive diagnosis based on fulfilling at least one clinical and one laboratory criteria in the updated Sapporo or Sydney criteria.[1] Clinical criteria include vascular thrombosis involving arterial, venous or small vessel in any tissue or organ; or pregnancy morbidity such as one or more unexplained deaths involving a morphologically normal foetus at or after 10 weeks of gestation, one or more premature birth of a morphologically normal infant before 34 weeks of gestation due to eclampsia or placental insufficiency or three of more unexplained consecutive spontaneous abortions before 10 weeks of gestation.[1] Laboratory criteria include presence of LAC, aCL IgG and/or IgM isotype in medium or high titre or anti-β2GPI IgG and/or IgM isotype in two or more occasions, at least 12 weeks apart. APS affects about 5 new cases per 100,000 persons per year with a prevalence of 20-50 cases per 100,000 persons per year.[1] The age groups most affected are the young and middle-aged with more females affected than males. The ratio of females to males are 1:3.5 for primary APS and 1:7 for secondary APS due to SLE.[1]

Primary APS is not associated with any underlying disease whereas secondary APS occurs in association with an underlying autoimmune disease, namely systemic lupus erythematosus. Presence of aPL in patients with systemic lupus erythematosus ranges from 10-30%. Besides, aPL may also be detected in association with infections, drugs and malignancy. However, the titres are usually low and transient and do not increase the risk of thrombosis or result in pregnancy morbidity. On the other hand, aPL may be present in about 1-5% of healthy individuals but are clinically asymptomatic.[1] Furthermore, the number of positive aPL determines the risk of thrombosis. The presence of a single aPL confers a lower risk of thrombosis or pregnancy morbidity compared to those with triple positivity. Of all the aPL, presence of LAC is strongly associated with APS.[2]

The key pathogenetic factor in APS is endothelial dysfunction. Antiphospholipid antibodies bind to membrane receptors in the endothelium which set off a cascade of events leading to thrombosis. β2GPI may be required in some cases for this process to occur. In APS, the synthesis of nitric oxide, which is important in vasodilation, is impaired. In addition, platelets and monocytes exhibit a prothrombotic phenotype in the presence of aPL. There is also dysregulation of vascular tone and activation of the complement cascade in the presence of aPL.[3]

The clinical manifestations of APS are variable ranging from cutaneous to visceral involvement. The most common clinical presentation is venous thrombosis. Cerebrovascular events are the most common manifestation of arterial thrombosis. Cutaneous signs may be the initial presenting signs and they are present in 4-55% of patients with APS.[4] The most common skin manifestation is livedo reticularis, followed by necrotic cutaneous ulcers, digital gangrene, subungual splinter haemorrhages, pseudovasculitic lesions, livedoid vasculopathy, atrophie blanche, Degos-like lesions and primary anetoderma.[4]

Subcutaneous papules and nodules as presentation of APS are rarely reported.[5,6] Ishikawa et al.[5] described four patients, two of whom had primary and secondary APS, respectively. These patients reported tender papule or nodule on the finger, sole and leg. Histopathological examination showed vessels with organised thrombi and surrounding neovascularisation. Farrant et al.[6] reported a patient with a history of deep venous thrombosis who had recurrent subcutaneous nodules which was complicated by hepatic vein thrombosis. Our patient also had recurrent subcutaneous nodules of his lower limbs for several months before diagnosis was made. As there are many differential diagnoses to consider for subcutaneous papules and nodules, a skin biopsy for histopathological examination is essential for definitive diagnosis.[5]

In general, abdominal aortic aneurysms (AAA) have a prevalence of about 2-12% and predominantly involve male gender above 65 years of age. These aneurysms are more commonly fusiform and infrarenal in origin.[7] Our patient although was young, had the traditional risk factors in developing aneurysm which included male gender, hypertension and being an active smoker. Interestingly he had saccular aneurysms at multiple sites of the aorta which suggested a different pathogenesis.

The pathogenesis of aneurysm formation includes immune-mediated processes leading to activation of matrix metalloproteinases (MMP) that degrade elastin in the aortic wall. The adaptive immune system is also involved.[8] Aneurysms have been reported as rare clinical manifestations of APS.[9] Studies have shown that the

Table I: Summary of published cases of primary antiphospholipid syndrome (APS) with aneurysms[9,10]

Age, Gender	Clinical manifestations	Arteries involved	aPL antibodies	Treatment
46, male (Current case)	***Persistent abdominal pain, recurrent subcutaneous nodules***	***Abdominal aorta (bifurcation, infrarenal), right common***	***LAC, IgG aCL***	***Warfarin***
34, female	Occlusion of small cerebral arteries	Carotid, middle cerebral artery	aPL	N/A
31, male	DVT, PE, migraine	Jejunal, pancreatic, superior mesenteric, renal	LAC, IgG aCL	Warfarin
20, male	PE	Pulmonary (saccular)	aCL	Coil embolisation, low dose heparin
38, female	Recurrent pregnancy loss	Splenic, hepatic, renal (saccular)	IgG aCL	N/A
42, female	Recurrent pregnancy loss, thrombocytopenia, haemolytic anaemia, stroke	Hepatic	LAC, IgG and IgM aCL	Warfarin
45, male	Kidney infarct, DVT, PE	Abdominal aorta (infrarenal) (saccular)	LAC, IgM and IgG aCL, anti-β2GPI, anti-phosphatidylserine	LMWH, warfarin, vascular surgery
51, female	Leg ischemia	Middle cerebral artery, abdominal aorta (infrarenal) (fusiform)	LAC	Heparin, warfarin
48, female	Recurrent pregnancy loss, recurrent DVT	Abdominal aorta (infrarenal)	LAC, IgG aCL, IgG anti-β2GPI	Heparin, aspirin, IVIg
67, male	Recurrent DVT, PE	Abdominal aorta	LAC	Warfarin
44, female	DVT, PE	Left main coronary	LAC, anti-β2GPI	Antiplatelet, anticoagulant
76, male	Stroke, idiopathic retinal vasculitis, aneurysms, neuroretinitis (IRVAN syndrome)	Retinal vessels	LAC, IgM and IgG aCL IgG and IgM anti-β2GPI, IgG and IgM anti-phosphatidylserine	warfarin
21, male	Superior vena cava syndrome	Coronary	N/A	Cardiac surgery
50, male	Multiple transient ischemic attack, amputation of toes bilaterally	Abdominal aorta	N/A	Vascular surgery
60, female	DVT, pregnancy loss	Abdominal aorta (fusiform)	LAC, IgG aCL, IgG anti- β2GPI	HCQ, aspirin
22, male	Pulsatile abdominal mass, migraine	Coeliac trunk, splenic, renal, superior mesenteric, right common iliac, external iliac (saccular)	LAC, IgG aCL	Aspirin, HCQ

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; LAC, lupus anticoagulant; aCL, anticardiolipin; aPL, antiphospholipid antibodies; anti-β2GPI, anti-β2 glycoprotein I; LMWH, low molecular weight heparin; IVIg, intravenous immunoglobulin; HCQ, hydroxychloroquine; N/A, not available

prevalence of aPL in AAA is 13.5% which is almost similar to other immune-mediated diseases such as systemic lupus erythematosus, giant cell arteritis and early rheumatoid arthritis.[8] It has been postulated that APS and aneurysm share similar pathogenetic mechanisms which are immune-mediated. Pro-inflammatory T cells are present in the tissue and peripheral blood of patients with AAA. B cells are responsible to produce aPL that enhances MMP-9 activity and/or induce accelerated degradation of elastin with arterial wall remodelling. Both processes lead to AAA progression. In addition, patients with aPL and AAA also have raised inflammatory markers. Generally, presence of aPL in cardiovascular disease and immune-mediated diseases have been associated with poor outcome.[8] Cases of primary APS with aneurysms are summarised in Table I. Majority of them (87.5%) were younger than 65 years with equal gender proportion. The most common affected vessel was the aorta. Other affected arteries included the coronary, carotid, retinal, middle cerebral, pulmonary, splenic and hepatic arteries. Of those cases whereby the morphology of aneurysms was described, saccular aneurysm was more common compared to fusiform aneurysm. The most common aPL detected was LAC, followed by antiCL and anti-β2GPI.

The treatment of APS involves antithrombotic therapy[1] with warfarin which is initially bridged with unfractionated heparin or low-molecular weight heparin till therapeutic anticoagulation is achieved. Studies have demonstrated that risk of recurrence of unprovoked venous thromboembolism was higher in patients with aPL and increases further in those with the same positive aPL on both occasions.[2] Lifelong anticoagulation is then necessary. In patients with venous thrombosis, target INR is 2.0-3.0 whereas for those with arterial thrombosis and/or recurrent thrombosis, a higher target INR of 3.0-4.0 or combined treatment of low dose aspirin with warfarin with target INR of 2.0-3.0 have been suggested.[1,2] A study has showed that combination therapy of low dose aspirin with anticoagulation reduced thrombosis recurrence to 6.9% compared to 23.7% on anticoagulation and 37.2% on antiplatelet therapy alone. Besides that, there is also longer time to recurrence with combination therapy.[2]

In cases of APS with aneurysms, caution must be exercised regarding the use of antithrombotic agents due to the risk of aneurysmal rupture. Treatments that have been utilised in cases of APS with aneurysms include warfarin, antiplatelet therapy, vascular surgery, heparin, hydroxychloroquine, coil embolism and intravenous immunoglobulin.[9,10] Excision

should be considered for cases with large aneurysms that are at risk of rupture. For smaller aneurysms, endovascular repair can be considered.[10]

Behcet's disease (BD), which is a diagnosis of exclusion, is an important differential diagnosis to consider due to the presence of subcutaneous nodules and thrombosis. Both fusiform and saccular arterial aneurysm formations at abdominal aorta, thoracic aorta, pulmonary, femoral, popliteal, brachial, iliac, mesenteric and subclavian arteries have been described in BD. Our patient scored 2 in the revised International Criteria for Behcet's disease (ICBD) criteria 2014 with a short duration of oral aphthosis of 3 months. In addition, there was no vasculitis or neutrophilic vascular reaction on histopathological examination, which are important features of BD. Furthermore, treatment of BD involves mainly immunomodulatory agents. Our patient responded well to anticoagulation, with no further development of other features of BD thereby refuting this diagnosis.

CONCLUSION

We described a case of APS in a male patient who presented with multiple saccular arterial aneurysms and subcutaneous nodules. A skin biopsy is deemed imperative to reach the diagnosis. In cases where the patient did not improve with treatment, a re-examination of the biopsy sample or a repeat biopsy is warranted. There should be a high index of suspicion with the combinations of unusual clinical presentations of APS, as a few organ systems can be affected concurrently. Early diagnosis and treatment lead to better clinical outcome and may avoid complications such as aneurysms.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

REFERENCES

1. Negrini S, Pappalardo F, Murdaca G, Indiveri F, Puppo F. The antiphospholipid syndrome: from pathophysiology to treatment. Clin Exp Med 2017; 17: 257-67.
2. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of antiphospholipid syndrome. Ann Rheum Dis 2019; 78: 155-61.
3. Velasquez M, Rojas M, Abrahams VM, Escudero C, Cadavid AP. Mechanisms of endothelial dysfunction in antiphospholipid syndrome: association with clinical manifestations. Front Physiol 2018; 9: 1840.
4. Pinto-Almeida T, Caetano M, Sanches M, Selores M. Cutaneous manifestations of antiphospholipid syndrome: a review of the clinical features, diagnosis and management. Acta Reumatol Port 2013; 38: 10-8.
5. Ishikawa O, Takahashi A, Tamura A, Miyachi Y. Cutaneous papules and nodules in the diagnosis of the antiphospholipid syndrome. Br J Dermatol 1999; 140: 725-9.
6. Farrant JM, Judge M, Thompson RP. Thrombotic cutaneous nodules and hepatic vein thrombosis in the anticardiolipin syndrome. Clin Exp Dermatol 1989; 14: 306-8.
7. Anagnostakos J, Lal BK. Abdominal aortic aneurysms. Prog Cardiovasc Dis 2021; 65: 34-43.
8. Duftner C, Seiler R, Dejaco C, Chemelli-Steingruber I, Schennach H, Klotz W, et al. Antiphospholipid antibodies predict progression of abdominal aortic aneurysms. PLoS One 2014; 9: e99302.
9. de Carvalho JF, Shoenfeld Y. Aneurysms in primary antiphospholipid syndrome: a case-based review. Clin Rheumatol 2021; 40: 3001 6.
10. Ehtuish EF, Mishra A. Multiple visceral aneurysms in antiphospholipid antibody syndrome - an unusual presentation. Br J Radiol 2008; 81: e184 7.