Anti-phospholipid syndrome leading to digital ischaemia and rare organ complications in systemic sclerosis and related disorders

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Key Indexing Terms: Raynaud's phenomenon, Systemic sclerosis, Anti-phospholipid syndrome, Clinical phenotype, Overlap syndromes, digital ulceration, critical digital ischaemia, posterior reversible encephalopathy syndrome, digital necrosis

Sources of support: None to declare

Conflicts of Interest: None of the authors report any conflicts of interest relevant to the content of this work

Word Count: 2497

Short title: APS in SSc and related disorders

Key points

- APS should be considered in all patients with digital ischaemic symptoms
- APS may be an important driver of SSc-related digital ulceration/necrosis
- Identification of SSc-associated APS opens up new therapeutic options for acute management and secondary prevention

Abstract

Antiphospholipid syndrome (APS) is an acquired, autoimmune thrombophilia that can occur as a primary disorder (with no associated disease) or secondary to infection, medication usage and autoimmune rheumatic diseases (ARDs). The association between APS and systemic lupus erythematosus (SLE) is well established and practicing rheumatologists check for APS antibodies in the routine assessment of SLE, particularly if clinical features such as thrombotic events or pregnancy loss are present. APS secondary to systemic sclerosis (SSc)-related disorders is less widely recognised and easily overlooked. We describe 5 cases that highlight the varied breadth of clinical manifestations of APS in the context of SSc and related disorders. These cases range from uncomplicated Raynaud's phenomenon, digital ulceration/necrosis, critical digital ischaemia/gangrene and rare internal organ complications of APS in SSc-spectrum disorders. To our knowledge, our cases include the first reported case of secondary APS contributing to digital necrosis in the context of RACAND syndrome (Raynaud's phenomenon, Anti-Centromere Antibodies, and Necrosis of the Digits) and the first reported case of secondary APS in SSc causing posterior reversible encephalopathy syndrome (PRES). The case series is accompanied by a comprehensive review of the literature relevant to each case. Rheumatologists should be alert to the possibility of APS in SSc-spectrum disorders and should routinely check APS antibodies in all patients at diagnosis, and again later in the disease course if new features emerge that could indicate the presence of thrombotic events or other recognised APS manifestations.

Word count: 237

Introduction

Antiphospholipid syndrome (APS) is an acquired, autoimmune thrombophilia in the presence of persistent antiphospholipid antibodies (aPLs)(1, 2). APS typically manifests as major arterial and/or venous thrombosis and/or obstetric morbidity; and it is these features that form the major classification criteria for APS(3). APS has several other recognised clinical manifestations, such as livedo reticularis, cutaneous necrosis, thrombocytopaenia, haemolytic anaemia, neuropsychiatric phenomena (e.g., transient ischaemic attacks (TIAs), cognitive deficits or white matter lesions), cardiac valve disease and nephropathy(2). APS can be classified as primary, whereby no underlying cause is identified, or secondary, in which there is an associated comorbidity, most commonly a systemic autoimmune rheumatic disease (ARD) or malignancy, or secondary to certain medications. The presence of aPLs in the context of systemic lupus erythematosus (SLE) was first noted in the early 1950s. Indeed, the APS itself was initially described in patients with ARD; the majority of whom had SLE(4, 5) . An APS screen forms an important part of the early diagnostic work-up of patients presenting with SLE or lupus patients developing atypical features later in the disease course(6).

Systemic sclerosis (SSc) is a rare ARD characterized by obliterative microangiopathy, autoimmunity/inflammation and aberrant tissue remodelling(7). Digital vasculopathy is an important clinical feature of SSc, manifesting as symptoms of Raynaud's phenomenon (RP) in virtually all patients and digital ulcers (DU) occurring in over half of patients at some stage during the disease course(8, 9). Digital vascular manifestations are generally assumed to be secondary to excessive vasospasm in response to cold exposure and the persistent ischaemic

effects of an evolving obliterative microangiopathy(10, 11). Whilst less common than in SLE, aPLs have been reported in SSc; although estimates of the prevalence have varied greatly depending on the methodological approach taken(12-19). Patients with SSc-spectrum disorders and APS antibodies have been shown to be at greater risk of digital vascular disease, pulmonary arterial hypertension (PAH), pitting scars, macrovascular disease and nailfold capillary abnormalities(13, 20). Digital vascular complications are typically overlooked in descriptions of clinical features of APS and are not included in APS classification criteria(3). We report five cases of APS occurring in SSc-spectrum disorders. Our cases have been chosen to highlight the heterogeneity in clinical presentation and severity, emphasising the need for consideration of primary or secondary APS in patients with digital vasculopathy and those with established SSc-spectrum disorders presenting with atypical features.

Cases

Patient 1

A 47-year-old, non-smoking, Caucasian female presented with a 3-year history of short-lived self-limiting episodes (~5 minutes) of painful acrocyanosis of the fingers. The attacks were not provoked by cold exposure. There was no history of thrombosis and/or pregnancy loss. She had strong radial pulses bilaterally, with equal arm blood pressures, and no identifiable stigmata of connective tissue disease. Nailfold capillaroscopy demonstrated normal capillary morphology and preserved capillary density (Figure 1A and B). Thermography of the hands revealed normal basal perfusion but delayed reperfusion of the left index finger at 5-minutes following a 1-

minute 20°C local cold challenge test (Figure 1C and D). Moderately high titre for anti-cardiolipin (aCL) IgM antibodies were identified on 2 occasions >12 weeks apart (72.5 MPL/mL and 51.1 MPL/mL, respectively). Anti-beta-2 glycoprotein 1 (anti-β2-GP1) IgM and IgG and lupus anticoagulant (LAC) were negative. There was a weak-positive anti-nuclear antibody (ANA) but extractable nuclear antigens (ENA) and double-stranded DNA antibodies were negative. Serum cryoglobulins and paraproteins were all negative/normal. Her HbA1c, lipid profile and plain films of the hands were normal. Anti-platelet therapy was commenced for suspected primary APS resulting in reversible digital occlusive microangiopathy and led to rapid and complete cessation of digital vascular symptoms, with benefits persisting at 6-months.

Patient 2

A 49-year-old, Caucasian male smoker (30 pack-year history) with an 11-year history of anti-PM-Scl antibody positive limited cutaneous systemic sclerosis (lcSSc), presented with a 2-week history of progressive necrotic ulceration and acute ischaemia of the left 5th finger (Figure 2A). Co-morbidities included type 1 diabetes and a history of previous transient ischaemic attacks. Blood pressure and pulses were equal in both arms. Hand X-ray showed widespread calcinosis cutis within the digits (Figure 2B). Persistent positive aCL IgM antibodies (titres 91.6 MPL/ml and 98.9 MPL/mL respectively) were identified >12 weeks apart, leading to a diagnosis of secondary APS. LAC and anti-β2-GP1 were negative. Treatment with warfarin, intravenous iloprost (11 days), phosphodiesterase type 5 inhibitor and optimisation of traditional cardiovascular risk factors stabilised the clinical picture with no further progression of digital necrosis and evidence of subsequent healing (see Figure 2C).

Patient 3

A 57- year-old, Caucasian female, with a 3-year history of anti-centromere positive lcSSc developed critical digital ischaemia and necrosis across multiple digits (Figure 3A). A history of 2 prior miscarriages was noted but she had no history of previous thromboembolism. Examination revealed puffy fingers, but no overt sclerodactyly, and necrosis of the 3rd-5th digital pulps bilaterally (see Figure 3A). Pulses and blood pressures were equal in both arms. LAC was positive on 2 occasions but aCL antibodies were negative. She was diagnosed with the rare subtype of SSc-spectrum disease–RACAND syndrome (Raynaud's phenomenon, Anti-Centromere Antibodies, and Necrosis of the Digits) with secondary APS. Treatment with warfarin and aggressive vasodilator therapy prevented progression of digital gangrene which was subsequently managed with surgical debridement of necrotic tissue (Figure 3B). There have been no further DU or digital necrosis over 4.5 years of follow-up.

Patient 4

A 54-year-old, non-smoking, Caucasian male had characteristic features of anti-centromere positive lcSSc with sclerodactyly, digital pitting, prior DU and typical abnormalities on nailfold capillaroscopy (Figure 3A and 3B). He had presented with worsening RP and acute right index and left middle finger subungal ulceration with necrosis, complicated by acro-osteolysis (Figure 3C). He had a history of previous large right parietal infarct (Figure 3D) and myocardial infarction. These events had been attributed to traditional cardiovascular risk factors including hypertension, hypercholesterolaemia, type 2 diabetes (managed with metformin) and atrial

fibrillation (anticoagulated with apixaban). He was admitted for intravenous iloprost for his digital ischaemia and found to be strongly positive for aCL IgG (64.6 GPL/mL and 99.1 GPL/mL on 2 occasions 12 weeks apart), in addition to a weakly positive anti-β2-GP1 IgG (15 MPL/mL), consistent with secondary APS. His anticoagulation was switched to warfarin with resolution of his digital ischaemic complications and no further episodes after 8 months follow-up.

Patient 5

A 61-year-old, Caucasian female, with long-standing lcSSc (anti-Scl-70 antibody) complicated by RP, recurrent DU, interstitial lung disease (ILD) (Figure 4A) and small bowel bacterial overgrowth, developed acute worsening of dyspnoea despite relatively stable ILD on cross-sectional imaging. Ventilation/perfusion imaging revealed a ventilation/perfusion mismatch consistent with acute pulmonary embolism, resulting in anticoagulation therapy with short-term warfarin therapy for 6-months. She subsequently presented with severe, sudden-onset headache and confusion. An MRI showed changes consistent with posterior reversible encephalopathy syndrome (PRES). A high titre aCL IgM antibody was identified on 2 occasions >12 weeks apart (104 MPL/mL and 102.6 MPL/mL). In view of her history of previous thromboembolic disease and episode of PRES, the patient was diagnosed with APS secondary to SSc and commenced on long-term anticoagulation with warfarin. Her PRES resolved and there were no further thrombotic events following initiation of warfarin.

Discussion

The cases described highlight the need to consider APS as a potential cause of digital ischaemia and other rarer organ-specific complications of APS occurring in the context of Raynaud's phenomenon and SSc-spectrum disorders.

In 4 of the reported cases, digital vasculopathy was a prominent feature. Digital ischaemia is an uncommon extra-criteria clinical manifestation of APS and not included in the core Sydney classification criteria (also known as the revised Sapporo APS classification criteria) for APS(3). Given the high prevalence of RP and prominence of digital ischaemic symptoms in SSc, APS could easily be overlooked as a cause of digital vascular compromise. Moreover, SSc is not typically considered as a cause of APS. The Euro-phospholipid project assessed the clinical manifestations of APS in 1000 patients from 13 countries, of which 53.1% had primary APS, while SLE was the most common secondary cause at 36.2%(21). In this cohort, SSc accounted for only 0.7% of cases(21). The most common presenting manifestation was DVT at approximately 32% of the cohort, trailed by thrombocytopenia at 22%, livedo reticularis at 20%, and stroke at 13%. Digital gangrene was noted to have occurred in 1.9%, at baseline with only a small number (n=14) of incident cases recorded during 5-years follow-up(21, 22). Digital gangrene and cutaneous necrosis, when present in APS, is generally a poor prognostic feature and often occurs in the context of Catastrophic APS (~70% of cases)(23). Digital necrosis was identified as an independent risk factor for mortality in APS in another retrospective survival analysis of 248 cases(24). A retrospective study of 45 patients presenting with digital necrosis over a 5-year period that excluded those with systemic sclerosis, identified primary APS as the

cause in 7% of cases(25). Other analyses of unexplained digital ischaemia have reported APS as the aetiology of digital ischaemia in a similar proportion (3-8%)(26, 27).

The European League Against Rheumatism have recently updated consensus guidelines on the management of APS(28). Consistent with the management instituted in case 1, primary thromboprophylaxis with low dose aspirin is recommended for symptomatic aPLs carriers (with or without other risk factors). Secondary thromboprophylaxis with lifelong vitamin K antagonist is initiated for APS if a thrombotic event has occurred with higher intensity therapy for arterial thromboembolism. In cases 2-4, warfarin was commenced in view of APS-related thrombosis as the likely driver of digital necrosis. Direct oral anticoagulants are generally avoided following recent reports indicating they are less effective in preventing thrombosis in APS(29, 30).

Case 1 relays that of an unusual mimic of Raynaud's like symptoms, with investigations attributing symptoms to a reversible microangiopathy due to primary APS. Excluding digital gangrene, the diverse spectrum of presentations of digital vasculopathy related to primary APS is largely limited to case reports and series. Table 1 presents an overview of previously published cases according to key digital complications.

Established systemic sclerosis and secondary APS overlap was observed in 4 of our cases. We identified the full gamut of aPLs including aCL IgM, aCL IgG, anti-B2 GP1 IgG, and LAC, highlighting the need for an extended testing to exclude APS in SSc. Three of our cases had a history of earlier venous (Case 5) or arterial (Cases 2 and 5) events that had been assumed to be

isolated events or related to conventional cardiovascular risk factors. Meta-analyses evaluating the frequency of aPLs in the context of SSc have reported a prevalence of ~13-14%, with considerable heterogeneity in study design(15, 31). Consistent with our cases, a range of aPLs antibodies have been reported in SSc with a 1-2% prevalence of LAC, 9% prevalence of ACL (with IgM and IgG isotype prevalence of 7.8 percent and 12.8 percent, respectively), and a 9% frequency of anti-B2-GP1(15, 31). Meta-analyses identified an association between aPL positivity in SSc and the occurrence of venous thrombosis and miscarriage, but had conflicting conclusions on the overall influence of APS antibodies on the prevalence of digital ischaemic complications(15, 31). Repeat testing of aPLs after 12 weeks only occurred in three studies included in these meta-analyses, and the average aPLs titres did not meet APS diagnostic criteria. A subsequent multi-centre study estimated a lower APS prevalence in SSc of ~4%(14). In this study secondary APS *was* associated with higher RP severity and/or the presence of active DU(14). Antibodies targeting β2-GPI were an independent factor associated with active DU both in univariate and multivariate analysis(14). All of our cases demonstrated enduring presence of medium-high titre aPLs after 12 weeks. It is possible that positivity to aPL at lower titres may contribute to microvascular occlusions through shared thrombogenic pathways with SSc.

As intravascular factors, platelet activation and thrombosis have long been suspected as contributing factors in SSc-related digital vasculopathy(32), it follows that the newly observed digital ischaemic features in SSc were presumably related to excessive vasospasm and the progressive obliterative microangiopathy of SSc. Treatment of SSc-associated RP and DU has

generally focused on vasodilators(33), with only a limited number of clinical trials focusing on anti-platelet or anticoagulant therapy for SSc-related vasculopathy(32, 34). Vascular thrombosis in APS is the result of a 'double-hit' scenario in which the underlying milieu of antibodies targeting phospholipid binding proteins is necessary, but insufficient in isolation for thrombosis. Proinflammatory and prothrombotic signalling driven by additional external factors (e.g. infection, drugs, trauma) result in endothelial injury and suppression of *in vivo* anticoagulant pathways, provoking thrombus formation(35, 36). Digital ischaemia in SSc in association with aPLs antibodies may therefore be precipitated by pro-inflammatory signalling that necessitates intervention with immunomodulatory and anticoagulant therapy to manage acute ischaemic lesions and prevent recurrence. In our cases, the introduction of long-term anticoagulation prevented further digital complications, supporting the likelihood of APS as the prominent factor driving microcirculatory thrombosis and subsequent digital complications.

The fourth case fulfils classification for both SSc and RACAND syndrome; which, to our knowledge, has not previously been reported in the context of aPLs. RACAND syndrome was originally coined following a series of four unusual cases mostly in elderly females, documenting the development of severe digital ischaemic lesions in the presence of ACAs, without dermal or visceral organ sclerosis(37). No identifiable histopathological changes were observed in arteries of amputated digits to account for the lesions(37). Whether this constellation of findings should be considered a distinct entity, or as part of the aetiopathogenic spectrum of SSc is debatable, although the apparent absence of overt

sclerodactyly despite ACA positivity may indicate the need to consider RACAND syndrome a distinct clinical entity(37-39).

Our final case of SSc with secondary APS resulted in the rare PRES (also known as reversible posterior leukoencephalopathy syndrome (RPLS)). There have only been a small number of reported cases of PRES in association with primary and secondary APS, often in association with high titre ACL IgM, as was found in our case(40-43). To our knowledge this is the first reported case of PRES occurring in the context of SSc and secondary APS. APS has previously been attributed as a risk factor for PRES in the context of normotension or mildly elevated blood pressure. It has been suggested that the pro-thrombotic state in APS engenders transient ischaemia, or causes increased vascular permeability of activation of vasoactive substances, common mechanisms linked to the general pathogenesis of PRES(42, 44).

Conclusions

In summary, our cases highlight the importance of considering APS in all patients presenting with digital ischaemic symptoms (particularly in the context of active ulceration or necrosis) or SSc patients with atypical features (particularly if there have been previous thrombotic events). APS antibodies should be routinely assessed at the time of SSc diagnosis and/or at the emergence of new features such as thromboembolic disease, new-onset digital ischaemic lesions and/or other potential extra-criteria features of APS such as PRES. The identification of secondary APS in SSc introduces the opportunity for additional therapeutic pathways beyond vasodilation for digital ischaemic lesions. SSc-associated APS should be managed according to

evidence-based recommendations to prevent future digital ischaemic events or new thrombotic events in other organ systems.

Funding This work did not receive any specific funding.

Conflicts of interest/Competing interests

Saion Chatterjee does not report any conflicts of interest. John Pauling has received speaker's honoraria and research grant support (>$10,000) from Actelion pharmaceuticals. John Pauling has undertaken consultancy work for Actelion pharmaceuticals, Sojournix Pharma and Boehringer Ingelheim; outside of the submitted work.

Ethics approval Written informed consent was obtained from each of the reported cases.

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Tables & Figures

Figure 1. Digital microvascular imaging studies in patient with primary APS and Raynaud's symptoms.

A, Low magnification (x50) image of nailfold revealing normal appearances with no peri-ungal erythema; B, High magnification (x200) image of nailfold demonstrating normal capillary morphology and preserved capillary density; C, Baseline thermal image of the hands revealing well perfused digits with preserved positive thermal gradient; D, Delayed re-perfusion of the left index finger following local cold challenge (20°C for 1 minute)

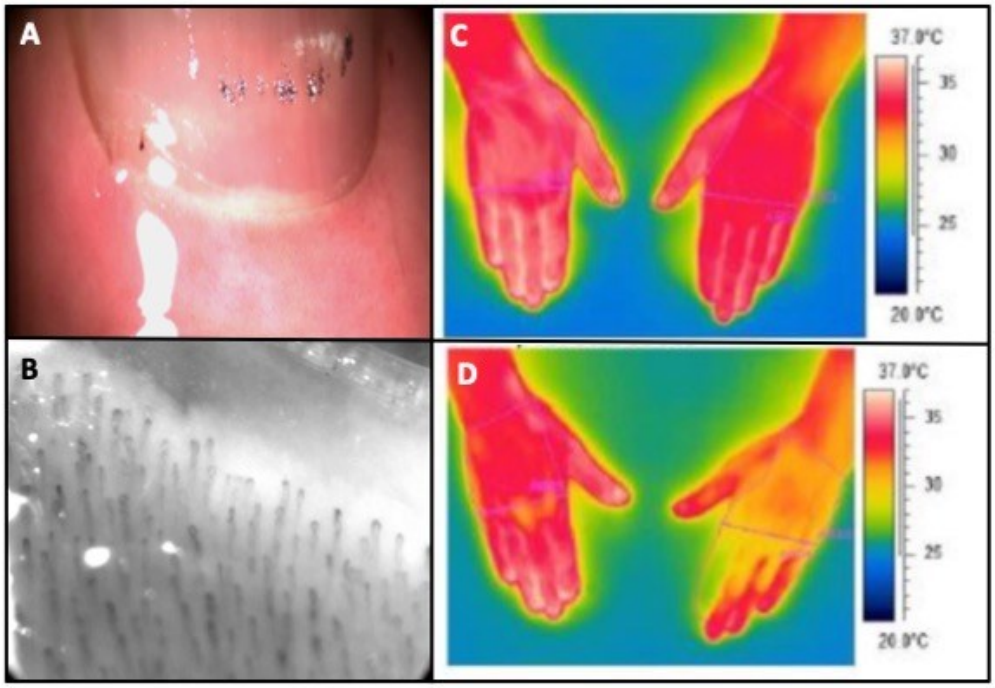

Figure 2. Progressive digital ischaemia and necrosis in a 49-year-old, male, smoker with lcSSc.

Digital necrosis extending across the dorsal aspect A(i) and pulp A(ii) of left 5th digit; B, Extensive calcinosis cutis (white arrows) on plain film of digits; C(i) and (ii), Arrested development of necrosis following introduction of warfarin and standard SSc-related digital vasculopathy therapy

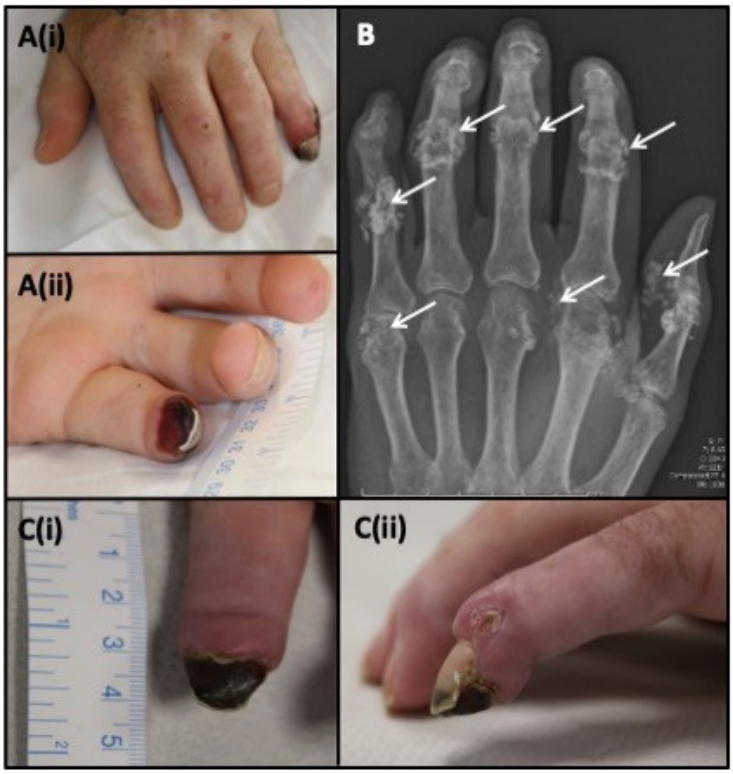

Figure 3. Digital necrosis in a patient with RACAND syndrome and positive LAC.

A, Digital ischaemic necrosis affecting 3rd to 5th digits; B, Digits following treatment with warfarin, intravenous iloprost and surgical debridement

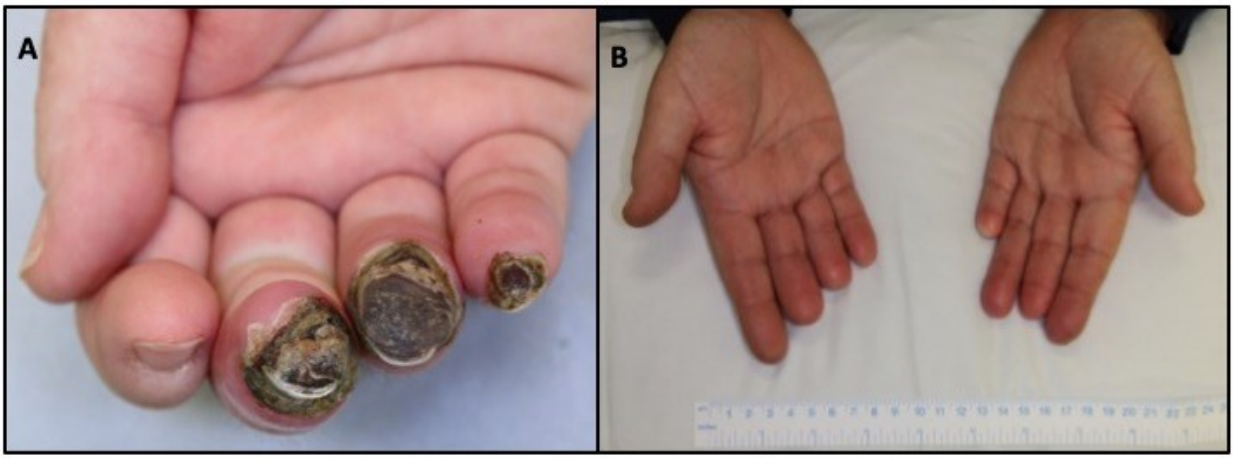

Figure 4. Cerebrovascular and digital vascular complications of secondary APS in a 54-year-old male with lcSSc. A, Image of the hands at presentation with sclerodactyly and subungal digital pitting; B, abnormal nailfolds with giant capillaries (black dashed arrows) and reduced capillary density; C, Acro-osteolysis of the 2nd and 4th distal phalanxes of the right hand (white arrows) after episodes of acute distal digital necrosis; D, Occipital cerebrovascular event causing homonymous quadrantanopia after warfarin replaced with DOAC.

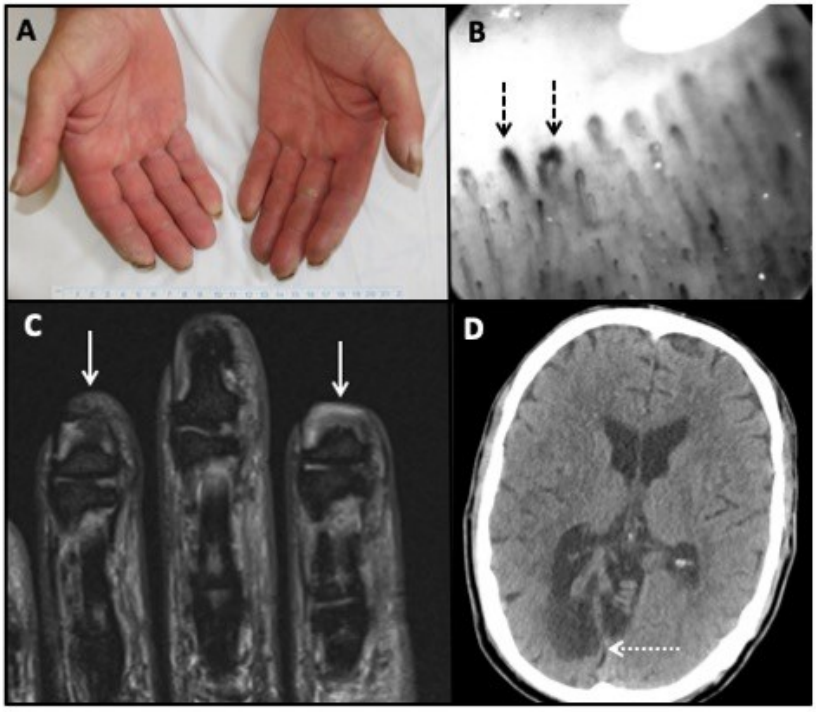

Figure 5. PRES in the setting of secondary APS in a 61-year-old female with lcSSc. A, Background non-specific interstitial pneumonia (NSIP) pattern demonstrated on CT chest; B, Posterior reversible encephalopathy syndrome (PRES) on CT head (white arrow).

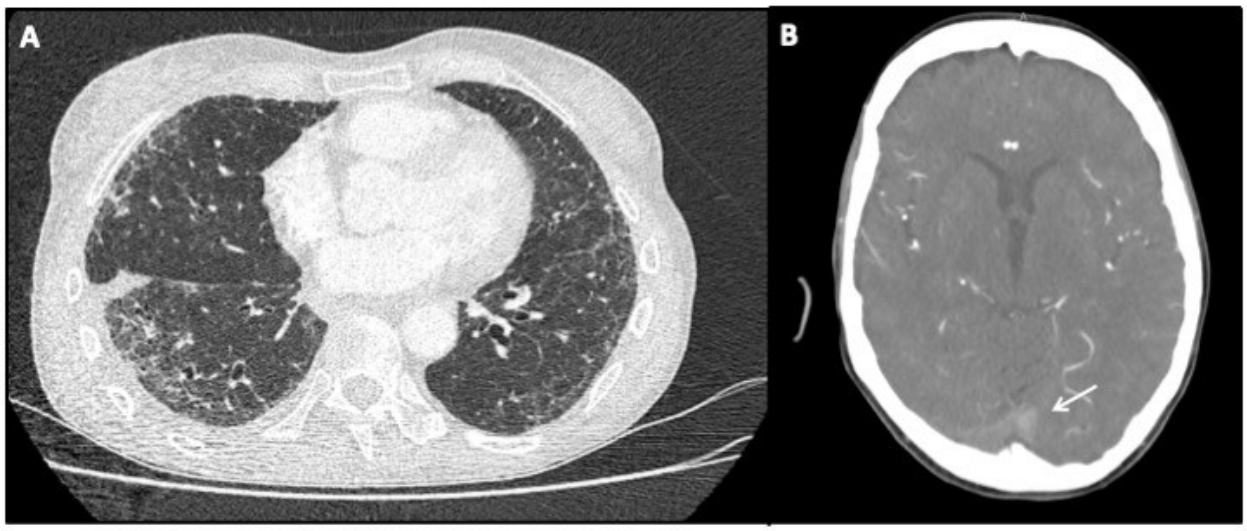

Table 1. Description of cases and management of the extra-criteria digital ischaemic manifestations related to primary APS.

Case Details	APS antibody	Management and Outcome
With Raynaud's (or Raynaud's-like) Phenomenon		
31F with RP and previous CVA and 3 miscarriages (mixed lengths of gestation) (45)	aCL IgG (high titre-130 HU), Other antibodies not measured‡	NR
27F with RP and previous transient visual loss and 4 miscarriages (mixed lengths of gestation (45)	aCL IgG (high titre-200 HU) and IgM (moderate titre) Others not measured‡	NR
9F with 2-weeek history of pain and cyanosis of left toes, in the setting of previous Raynaud's like symptoms (46)	aCL IgG (high titre-125 GPL)*	Vasodilators, including IV iloprost with resolution and no recurrence at 20-months of follow-up
With Digital Ulcers (DU)		
60M with bilateral intermittent claudication and non-healing ulcer of right toe, and 2-year history of RP (48)	LAC	Short-term anticoagulation and long-term dual-antiplatelet therapy. Endovascular therapy for aortic involvement. Resolution and no recurrence at 12-months of follow-up
With other digital ischaemic symptoms		
8-month F with toe discolouration (49)	aCL IgG (high titre-100 GPL)^ ‡	Anticoagulation (short-term) and antiplatelet (long-term) with resolution of symptoms, follow-up NR
4F with painful discolouration of digits (49)	aCL IgG (moderate titre-33 GPL)^ ‡	Immunosuppression & antiplatelet therapy. Symptoms resolved after 1 week of therapy, aCL normalised after 6 weeks, further follow-up NR
38F with episodes of pain in the right index finger (50)	aCL antibodies*‡	Anticoagulation and antiplatelet therapy. Resolution of digital symptoms, follow-up NR
41F with acute digital ischaemia of left foot and previous DVTs and PE (51)	aCL IgG (high titre-61 GPL)^ LAC^	Anticoagulation (INR>3) and antiplatelet therapy, alongside vasodilators. Improvement in ischaemic lesions (after increasing target INR and IV vasodilators).
23M (smoker) with 3-month history of pain and progressive cyanosis of left 4th toe (52)	aPLs (not specified)*	Anticoagulation (INR2.5-3) with resolution and no recurrence at 6-months of follow-up
50F with 2-week history of discolouration and pain of left digit/hand (53)	aCL IgM (high titre-73 MPL)^ anti-β2GPI IgG (high titre-63 GPL)^	Anticoagulation (INR2-3), antiplatelet therapy and hydroxychloroquine. Switch from anti-TNF to anti-IL-12/23. Resolution and no recurrence at 57-months of

	Prolonged dRVVT (ratio 1.55)	follow-up (39-months without anticoagulation)
With digital ischaemic necrosis		
77M with 2-week history of digital ischaemia, complicated by necrosis, and previous DVT and CVA (54)	ACL IgG (positive-49 HU)* LAC*[ǂ]	Resolution after anticoagulation with no recurrence at 6-months
64F with digital necrosis of multiple fingers and toes, and previous miscarriages (3 of unknown gestation) and cerebellar infarcts on CT (2) (55)	Anti-PT*	Initial antiplatelet therapy with relapse of digital necrosis. Aanticoagulation (INR 3-4) initiated with resolution and no recurrence.
73F with digital ischaemia/gangrene (hands and feet) (56)	LAC	Anticoagulation with vasodilators. Gangrene resolved (some onrgoing autoamputation) with no recurrence at 6-months
70M with bilateral digital necrosis with a background 2-month history of RP (47)	anti-β2GPI IgG (high titre-93.80 and 205 GPL ,12 weeks apart)	Anticoagulation with improvement, and no recurrence at 9-months

*Repeat testing at 12-weeks not described

^Repeat testing occurred, but no further details provided

[ǂ]Case report prior to updated Sydney classification criteria (2006)

aCL, anti-cardiolipin antibody; aPLs, anti-phospholipid antibodies; anti-β2GPI, anti-beta-2 glycoprotein 1 antibody; anti-PT, anti-prothrombin antibody; CT, computed tomography; CVA, cerebrovascular accident; dRVVT, dilute Russell viper venom time; DVT, deep vein thrombosis; F, female; GPL, IgG phospholipid units HU, Hammersmith units; INR, international normalised ratio; IgG, immunoglobulin G, IgM, immunoglobulin M, IV, intravenous; LAC, lupus anticoagulant; M, male; MPL, IgM phospholipid units NR, not reported; PE, pulmonary emboli; RP, Raynaud's phenomenon