A review of the development of gangrene in patients with Systemic Lupus Erythematosus – a 44-year follow-up study

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Data sharing
Following any reasonable request, the authors are very happy to share the data upon which this publication is based.

Abstract

Objectives: This review addresses the prevalence of gangrene in a cohort of SLE patients, aiming to find common clinical and serological features, risk factors and triggers, as well as review the acute and long-term management of gangrene in these patients.

Methods: We reviewed 820 patients with SLE attending the SLE Clinic in UK tertiary referral center, followed up over 44yrs, assessing demographics, clinical and serological features, treatment in the acute phase, outcome and long-term management.

Results: Eight out of 820 patients (0.97%) have developed gangrene with the age of onset of disease ranging from 12 to 26 years. The first episode of gangrene ranged from presentation to 27 years after SLE onset, with a mean duration of SLE at the onset of the gangrene of 15.5 years. Anti-phospholipid (PL) antibodies were over-represented in the patients with gangrene. All had active SLE at the time the gangrene developed. All patients were treated with intravenous (IV) iloprost infusions, antiphospholipid-positive patients were anti-coagulated, most of them staying on long term anticoagulation therapy. Underlying possible triggers were treated accordingly. Two patients who did not respond to the initial treatment needed further immunosuppression. All patients suffered digit loss. Conclusion: Although rare, gangrene is a sinister, potentially late developing complication of SLE. It is associated with anti-phospholipid antibodies, active disease, and other possible contributors such as infection and cancer. Besides anticoagulation therapy, steroids and iloprost, further immunosuppression may be needed to stop the evolution of gangrene.

Key words

Systemic lupus erythematosus, digital gangrene, antiphospholipid syndrome, warfarin, immunosuppression

Key Messages

Gangrene is a rare manifestation and/or complication of SLE with potentially serious long-term morbidity.

Anti-phospholipid (PL) antibodies were over-represented in the gangrene patients.

Aggressive early treatment and long-term anti-coagulation may be the optimal therapy for these patients.

Introduction

Gangrene is a well-recognised complication of diabetes, peripheral arterial disease, frostbite and meningococcal disease amongst other conditions but is mercifully rare in patients with systemic lupus erythematosus [SLE]. Fourteen years ago [1] our group reported five patients who had developed digital gangrene [and another two with 'near gangrene']. We have now reviewed the histories of 820 [SLE] patients seen in our lupus clinic for long term follow up between January 1978 and June 2022 and identified eight patients [0.97%] who have developed digital gangrene. We have tried to identify the possible trigger factors and clinical and serological profiles of these individuals. We have reviewed their initial treatment and reflected on their long-term management and outcome. We have also reviewed the literature on this topic.
Gangrene in SLE patients is rare and most reports describe individual patients [2], [3], [4], [5] Reports of its prevalence in SLE cohorts are scarce, although Liv et al did report [6] 18 patients [out of 2684 SLE patients] from China thirteen years ago.

Methods

Using both hard copy patient notes and electronic records [available from 2003] we have identified all the patients in our SLE cohort [established in January 1978 by Dr Michael Snaith]. We collected information on their sex, ethnicity, age at diagnosis [according to the revised criteria of the American College of Rheumatology [7]) age at development of gangrene, history of obvious triggering events [if any], treatment at the time the gangrene developed, treatment of the gangrene itself, serological profile, short-term outcome [numbers of digits and other tissues lost] and long-term [> 40 years in some cases] outcome.

This study is in essence an audit and University College London does not require formal ethical approval for this type of anonymised study. Most of the patients reported here have been previously described in the literature [at an earlier stage of their disease]. The one patient who has never previously has given written permission for her history to be included.

Results

In the 44 years since our SLE patient cohort was started, gangrene has occurred in 8 out of 820 patients (~1 %), The details of the individual cases

are shown in Table 1. Five of these patients were initially reported in the 2008 report [1]. Most patients were female, with just one male patient, which is in agreement with the gender distribution of SLE in our cohort. Six out of eight patients were Caucasian (75%), one each was south Asian and Black. This ethnic distribution is slightly different from the SLE cohort but not statistically significative because of the small number of patients with gangrene. The mean age of onset of disease was 17.9 years (12-26 years). The first episode of gangrene ranged from presentation in two cases (Case 1 and 4) to 27 years after the disease onset (Case 8), with a mean duration of SLE before the onset of the gangrene of 15.5 years, agreeing with previous reports [6].

Anti-phospholipid (PL) antibodies were positive in five out of the eight reported patients (only cases 2, 4 and 7 were negative). Among these patients, three were triple positive with anti-cardiolipin (ACA), anti beta2 glycoprotein 1 antibodies and lupus anti-coagulant (LAC). Two others were ACA positive and one was ACA and LAC positive. IgG antibodies were present in four out of these five patients (80%) and IgM antibodies were positive in three patients (60%). LAC was positive in three out of five patients (60%) who had positive anti-phospholipid antibodies. Five out of eight patients had anti-RNP antibodies, but none had clinical features of SSc and/or myositis (62.5%)

All these patients had cutaneous involvement (three of them with vasculitis) except for case 8. Four patients out of eight had severe Raynaud's phenomenon and six out of the eight had renal involvement. When the gangrene developed, all of them had active SLE with raised anti-dsDNA antibodies and low C3 or a low C3 alone (Case 5).

We looked for possible triggers or risk factors that might have contributed to the development of gangrene. Two of the affected patients with anti-PL (Cases 1 and 5) were smokers, two patients had raised cholesterol (Case 3 and 7) and one patient (Case 1) subsequently developed deep venous thrombosis (DVT) and pulmonary embolism (PE). One patient had positive cryoglobulins type III at the onset of gangrene (Case 6). Septicaemia was present in two patients (Case 2 and 5), with other two having mild infections (Case 4 and 6).

All patients were treated with continuous intravenous (IV) iloprost the maximum tolerated dose for 3–5 weeks and six of them were given steroids. Additional treatment varied according to the precipitating cause, including antibiotics when infection was present. Anticoagulation was initiated with IV heparin infusion or subcutaneous low molecular weight heparin

(enoxaparin 1mg/kg twice daily) with subsequent conversion to long-term warfarin therapy, if they had anti PL antibodies.

A detailed description of cases 1 to 5 has already been published [1]. In addition, case 7 and 8 were recently described [8]. The remaining patient (Case 6) is the most recent case of gangrene in this cohort [figure 1- She presented with severe gangrene of fingers and toes, with mild positive anticardiolipin IgM antibodies and LA slightly elevated, high levels of anti-dsDNA antibodies and low complement levels. She had an history of previous subclavian vein thrombosis with no APS antibodies at that time. At the time of gangrene onset, she had a urinary infection (E. Coli/Mycoplasma), with no septicaemia, and type III cryoglobulinemia. She was treated with anticoagulation therapy, IV methylprednisolone and iv continuous infusion of iloprost, fifteen sessions of plasma exchange, cyclophosphamide and Obinutuzumab (she had had a previous allergic reaction to Rituximab). Gangrene progression stopped but she has started to suffer autoamputation of fingers and toes. She was reviewed in the SLE Clinic recently and she has dry gangrene of 2nd to 5th fingers on the right hand, all fingers of the left hand; all of the toes in her left foot; and 4th and 5th toes of the right foot. She continues on enoxaparin, 1mg/kg, twice daily.

With the exception of Case 2 and 4, all the patients stayed on long-term anticoagulation therapy with warfarin or enoxaparin. Neither case 2 or 4, had anti-PL antibodies. Case 4 stayed on anti-aggregating therapy.

In respect of follow-up, reviewing all 8 patients, only two had a second or further episodes of gangrene. Case 4, with no associated anti-PL antibodies, had three episodes of critical ischaemia and gangrene of fingers and toes over a 42-yr course of disease. He was on anti-aggregating therapy with aspirin 75mg/day but reforced to go onto anticoagulation therapy. The last and 4th episode of the disease was in context of the development of Hodgkin lymphoma and cryoglobulinemia type III. Case 8 had a second ‘hit’ of the disease with a necrotic left big toe and tip of the 3rd toe. She had had a recent trauma of the left leg three months before with no complete recovery from that lesion. She was on long term anticoagulation therapy with warfarin. Case 6, being our most recent case, needs further follow up to know how the disease will evolve. Two of the patients have died with the cause of death not being directly related to SLE disease activity.

Discussion

Peripheral digital gangrene is a rare manifestation of SLE, being particularly unusual as a first presentation of SLE. [3],[6],[9] Although there are no recent reports about the prevalence in SLE patients, three previous studies

reported a prevalence of gangrene in SLE patients between 0.6% and 5.8% [1], [6], [10]. In our cohort the prevalence was about 1%, with only two patients having gangrene as a presentation of SLE disease.

Long duration of lupus (>/= 4 years) is a known risk factor for the development of gangrene [6],[9]. With a mean duration of SLE before the onset of the gangrene of 15.5 years, the development of gangrene in our cohort was consistent with previous reported studies, with most patients having the first episode of gangrene at a late stage of the disease.

Causes of gangrene in the context of SLE are unknown and probably multifactorial, and the underlying mechanism is likely to be complex, possibly including vasculitis and infectious disorders causing vasculitis, mechanical and obstructive disorder, premature atherosclerosis, vasospasm, overlap syndrome, hypercoagulability and thrombosis related to anti-PL antibodies or embolus. All of them may contribute to the development of gangrene [1], [6].

In our cohort of SLE patients with gangrene, anti-PL antibodies seemed to have an important role in the development of gangrene, being over-represented in this group (ACA IgM antibodies were present in 60% of patients, ACA IgG in 80% and LA 60% compared to ACA IgM in 9%, ACA IgG 21% and LAC 14% in our SLE cohort overall – unpublished observation).

All the patients in our ‘gangrene cohort’ had active disease at the time the gangrene developed, with high levels anti-dsDNA antibodies and/or low complement, which implies an important role for disease activity tin the development of gangrene. But clearly few patients with active disease develop gangrene, thus other risk factors are clearly involved.

Previous cutaneous involvement has been reported as a possible predictive factor for development of gangrene [6], especially Raynaud’s phenomenon, which was present in 50% of our cohort. However, neither in our own experience or from the literature, has any compelling ‘clinical profile’ of those SLE patients more likely to develop gangrene emerged. Two out of our eight patients had an overlap of autoimmune diseases (Sjogren’s and autoimmune thyroid disease).

Because of the low prevalence of patients developing gangrene in the context of SLE, evidence for treatment of gangrene in this context is limited. Based on the evidence for treating of other causes of peripheral ischaemia such as atherosclerotic peripheral vascular disease, ischaemic diabetic disease, ulcers and thromboangitis obliterans, the goal of treatment is to stop the

progression of the disease, to remove the causative factors, to prevent secondary infections and to remove nonviable tissue. It is also agreed that the management of this critical disease should involve a multidisciplinary approach. [11]
The main treatment approach, suggested previously by Liu et al and others [6], includes early treatment with vasodilatation, steroids, immunosuppressive drugs, lipid lowering agents, and anticoagulation therapies (especially in those patients whose lupus is accompanied by antiphospholipid syndrome).
Treating the underlying condition, aiming to reduce disease activity is an important factor in our patients, with immunosuppression having an important role. Steroids and immunosuppression seemed to be effective and further immunosuppression with cyclophosphamide and other, including B cell depletion such as rituximab, have now a role in patients with immune disease not responding to the initial therapy.
Although some authors question if i.v prostaglandins, such as iloprost, are necessary as the initial management of gangrene in lupus as reported by Jeffery et al. [1]; the majority of reported patients had iv iloprost with good response, pain relieve and fewer side effects. Other type of drugs such as trimethaphan, sodium nitroprusside, nitroglycerine ointment, intravenous alpha blocker and recombinant tissue plasminogen activator, have not been tested in clinical controlled trials but may be use in in some of the literature [12].

Most cases of gangrene associated with SLE in our cohort responded to treatment with IV Iloprost, anticoagulation and steroid therapy (only two patients did not receive need steroid therapy), with case 3 and case 6 being the two major exceptions. They had a much more severe disease course and failed to respond adequately to these types of treatments. Case 3 continued to have progressive peripheral ischaemic lesions after this treatment and was given additional immunosuppression with rituximab in combination with methylprednisolone and cyclophosphamide. The progression of the ischaemic lesions stopped and there was a fall in her anti-dsDNA and anti-PL antibodies, with normalization of her complement levels. In case 6, after further immunosuppression, including Obinutuzumab, gangrene progression stopped but with severe damage to her extremities. She remains on long term anticoagulation therapy. These two cases confirm the importance of immunosuppression in patients not responding to other therapies.

We could not find any recent studies in the literature reporting long term follow-up of SLE patients who developed gangrene. There is little evidence available to help guide us about the potential for recurrence of gangrene in SLE patients. Previous studies showed that the prevalence of a first

thrombosis in aPL-positive patients has been estimated at 1% per year and recurrent events in patients not on anti-coagulant therapy at 10–29% per year [x]. Although one episode of the disease may be enough to cause severe damage, a second or further episode seems to be even rarer than the first episode. We report just two out of eight patients having developed a recurrence in our cohort. It seems, indeed, to be linked to another factor, including infection, cancer, trauma or sub-therapeutical/non anticoagulation therapy.

It seems likely that aggressive early treatment followed by long term anti-coagulation is the optimal therapy for these patients. Whether the anti-coagulation needs to be continued in those lacking anti PL antibodies is unknown.

Patients whose SLE is complicated by gangrene is rare but a potentially devastating condition. It requires high index of suspicion, so that treatment can be initiated as soon as possible. Recurrence of the problem is also rare but the damage it can do in terms of lost digits and other soft tissues is profound.

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Patient Details	Case 1 15yrs AAO Female; Caucasian	Case 2 18yrs AAO Female; Caucasian	Case 3 15yrs AAO Female; Caucasian	Case 4 16yrs AAO Male; Caucasian	Case 5 26yrs AAO Female; Caucasian	Case 6 12yrs old AAO Female; Black Caribbean	Case 7 23yrs AAO Female; Asian Indian	Case 8 15yrs AAO Female; Caucasian
Lupus features (clinical)	Cutaneous(vasculitis) Raynaud's arthralgia Renal (mesangial cell proliferation) Partial complex seizures Anemia Serositis, Transaminitis	Cutaneous (vasculitis) Raynaud's arthralgia Renal (class IV) Fits, depression, headache Lymphopenia	Cutaneous (ulcers, alopecia) Raynaud's Arthritis CNS (migraine) Lymphopenia PNS (mononeuritis multiplex, sensory neuropathy) Respiratory (low transfer factor)	Cutaneous (photosensitivity, ulcers) Raynaud's Erosive Arthritis Psychosis Neutropenia Thrombocytopenia	Cutaneous (vasculitis, ulcers, alopecia, rash) Serositis Class IV LN Haem (lymphopenia, neutropenia, thrombocytopenia)	Malar rash, arthritis, pleurisy, serositis Autoimmune hepatitis Pericarditis Class IV LN Probable APS	Rash fever, alopecia Serositis Arthritis	LN APS – triple positive
Lupus features (serological)	ANA positive Anti-DNA positive Low C3 ENA negative ACA positive (IgG and IgM) B2GP1 positive LAC positive	ANA positive Anti-DNA positive Anti-RNP&-La positive ACA negative LAC negative	ANA positive Anti-DNA positive Low C3 AntiRNP positive ACA positive (IgG) B2GP1 positive LAC positive	ANA positive Anti-DNA positive Low C3 AntiRO positive ACA negative LAC negative	ANA positive Anti-DNA negative Low C3 AntiRNP positive ENA negative ACA positive (IgM and IgG) LAC negative	Positive ANA dsDNA positive RNP/anti-SM positive Low C3 Mild positive ACA IgM LAC positive (Slightly elevated)	Positive dsDNA Low C3 Positive AntiRo, La, SM and RNP APS antibodies neg But in 2003: APS with stroke. B2GPI high IgG	Positive dsDNA Low C3 APS triple positive ENA negative AntiRNP positive ENA negative
Other factors	Smoker Deep venous thrombosis/ Pulmonary embolism Autoimmune thyroid disease	Meningococcal septicaemia	Hyper-cholesterol	Sjogren's Rheumatoid factor positive Bronchiectasis Recurrent cellulitis Conjunctival ulcers Cryoglobulinemic type III Classic Hodgkin Lymphoma	Smoker Klebsiella septicemia Disseminated intravascular coagulation	Congenital heart block Previous partial left subclavian vein thrombosis E. Coli/Mycoplasma in urine Cryoglobulins Type III	Hyper-cholesterol	Heart disease (valvopathy) 2nd hit: Trauma 3 months before
Disease duration of SLE at gangrene onset	0 years	5 years	20 years	0,18, 23, 42 years	24 years	24 years	24 years	27, 29 years
Gangrene extent	Gangrene of fingers	Gangrene of fingers	Severe gangrene of fingers/toes; Necrotic elbow ulcers; Bilateral palmar artery thrombosis	3x gangrene fingers/toes Ischemic ulcer on right middle fingertip	Dry gangrene of hands and feet	Gangrene of hands and feet	Gangrene of fingertips both hands	Digital ischemia Left big toe and tip of the 3rd toe necrotic
Outcome	Loss of 2nd and 4th fingertips	Autoamputation of fingertips	Auto-amputation of left 1st, 3rd, 4th and 5th fingertips; and three finger toes in both feet	Autoamputation of little fingers in both hands and 2nd and 3rd right finger toes	Right forefoot amputation	Dry gangrene of 2nd – 5th fingers right hand, all fingers left hand; all fingers left foot; 4th and 5th finger toes	Auto amputation of index and middle finger	Right foot amputation
Long term AC therapy/Other	Warfarin	?	Warfarin	Aspirin	Warfarin	Enoxaparin	Warfarin	Warfarin (including during second hit)
Status	Alive	Deceased (COVID)	Alive	Alive	Deceased (Cardiorenal syndrome)	Alive	Alive	Alive

Table 1 - Demographics, clinical and serological features, other possible contributing factors, SLE disease duration at the onset of gangrene, clinical extent and outcome of gangrene, and long-term management of gangrene patient's cohort

All patients ANCA, Anti-Scl-70/Topoisomerase I and viral hepatitis negative | AAO – Age at onset of SLE; AC – anticoagulation; ACA – anticardiolipin antibody CNS – Central Nervous System; CPI – Critical Peripheral ischemia; DD – Disease duration of SLE; DIC – disseminated intravascular coagulation ; LAC – Lupus anticoagulant; LN – lupus nephritis

Figure 1 to 6: Patient 6 gangrene evolution. She presented with severe gangrene of fingers and toes, with mild positive anticardiolipin IgM antibodies and LAC slightly elevated, high levels of anti-dsDNA antibodies and low complement levels; an history of previous subclavian vein thrombosis with no APS antibodies and she had a urinary infection and type III cryoglobulinemia at the onset of gangrene. Although the gangrene had stopped after anticoagulation therapy, IV methylprednisolone and iv continuous infusion of iloprost, fifteen sessions of plasma exchange, cyclophosphamide and Obinutuzumab, she suffered severe damage and autoamputation of fingers and toes.