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

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Abstract

Objectives: This review addresses the questions of what happens long-term to those SLE patients who develop gangrene. It also seeks to find common clinical and serological features, risk factors and triggers and how best to manage this challenging complication.

Methods: We reviewed 850 patients with SLE attending a UK tertiary referral center, followed up over 44yrs, assessing their demographics, clinical and serological features, treatment in the acute phase, their long-term outcome and long-term management.

Results: Ten out of 850 patients (1.2%) developed gangrene; the mean age of onset was 17 years (range 12-26yrs) Eight out of ten patients had a single episode of gangrene. One of the other two was not willing to have anticoagulation. The first episode of gangrene ranged from presentation to 32 years after SLE onset, mean duration of SLE at the onset of the gangrene was 18.5 years SD 11.5 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, and the antiphospholipid-antibody positive patients were anti-coagulated, most staying on long term anticoagulation . Underlying possible triggers were treated appropriately. 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 rarely recurs. It is associated with anti-phospholipid antibodies, active disease, and other possible triggers such as infection and cancer. Anticoagulation therapy, steroids and iloprost, and 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]. Fifteen years ago [1] our group reported five patients who had developed digital gangrene [and another two with 'near gangrene']. Two further patients were reported later. We have now reviewed the histories of 850 [SLE] patients seen in our lupus clinic for long term follow up between January 1978 and March 2023 and identified ten patients [1.2%] who have developed digital gangrene, three of whom have never been reported previously 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. Notably absent from previous publications is information about the very long-term outcome for the patients and we now address the critical question of whether the gangrene recurs.

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.

Results

In the 44 years since our SLE patient cohort was started, gangrene has occurred in 10 out of 850 patients (1.2 %), The details of the individual cases are shown in Table 1. Five of these patients were initially reported in the 2008 report [1]. We now add an additional five patients and an extra 15 years of follow-up for the original patients. Intriguingly six out of the ten patients

developed their SLE as adolescents and importantly overall in only two patients did a further recurrence of their gangrene occur.

Most patients were female, with just one male patient, which is in agreement with the gender distribution of SLE in our cohort. Seven out of ten patients were Caucasian (70%), one was south Asian and two Black. This ethnic distribution is slightly different from the SLE cohort as a whole but not statistically significative because of the small number of patients with gangrene. The mean age of onset of disease was 16.4 SD = 6.4 years (12-26 years). The first episode of gangrene ranged from presentation in two cases (Case 1 and 4) to 29 years after the disease onset (Case 10), with a mean duration of SLE before the onset of the gangrene of 17.1, SD = 11.3 years, agreeing with previous reports [6].

Anti-phospholipid antibodies [APAb] were positive in seven out of the ten 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). Three others were ACA positive and two of which were also LAC positive. LAC was positive in six out of those eight patients (75%) 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%). In contrast, one patient had [focal] myositis without any anti-RNP or myositis-specific antibodies being detected.

All these patients had cutaneous involvement (three of them with vasculitis) except for case 8. Five patients out of 10 had severe Raynaud's phenomenon and five also had renal involvement four being WHO class IV. When the gangrene developed, all of them had active SLE clinically and/or serologically.

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) Two patients had positive cryoglobulins type III at the onset of gangrene (Case 6). Septicaemia was present in three patients (Case 2, 5 and 9), with two others having mild infections (Case 4 and 6).

All patients were treated with continuous intravenous (IV) iloprost the maximum tolerated dose [usually 0.5-2 nanograms/kg/minutes; given for 12-24 hours daily] for 3–5 weeks and eight of them were given steroids starting with IV methylprednisolone infusions 0.5-1gm x 3 IV daily followed by

reducing oral prednisolone from 40mg/day reducing to a maintenance dose of 7.5mg/daily over 1-2 months. 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 APAb.

A detailed description of cases 1 to 5 has already been published [1]. In addition, cases 7 and 8 were recently described [8]. Of the remaining patients (Case 6) [see figure 1] presented with severe gangrene of fingers and toes, with mild positive anticardiolipin IgM antibodies and a positive LA, 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 autoamputated several fingers and toes, notably 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.

Case nine presented dramatically with a sagittal venous thrombosis and was found to have a positive ANA and anti-dsDNA and a lupus anticoagulant. The subsequent development of proteinuria [plus arthritis and discoid lupus] lead to a renal biopsy, which showed a WHO type II glomerulonephritis. Unfortunately, she bled into the kidney and eventually had to have a nephrectomy. During the next 15 years of her lupus her major manifestation was severe discoid lupus which responded inadequately to steroids, mycophenolate, azathioprine and rituximab. She became hypogammaglobulinaemic, almost certainly due to the rituximab. She was tried on benlysta which in turn triggered a significant neutropenia. This led to septic shock secondary to a pseudomonas bacteraemia and brought on chronic renal failure. While in the intensive care unit she developed an acute onset of gangrene in the left thumb, left thigh and all of her toes bilaterally.

Case ten presented with idiopathic thrombocytopenic purpura [ITP] aged 16 [IIP] which did not respond to steroids, but did to a splenectomy. Three years later aged 20 she was found to be ANA and anti-dsDNA antibody positive. She also had a positive LAC and moderately raised IgG anticardiolipin antibody levels. Over the next 18 years she continued to flare intermittently and was treated with hydroxychloroquine, low-dose prednisolone and

azathioprine. When she developed recurrent superficial thrombophlebitis warfarin later switched to rivaroxaban was added.

Twenty-nine years after her SLE diagnosis while she was serologically [though not clinically] very active, overnight she developed critical ischaemia in three fingertips of her left hand. Prompt treatment with intense intravenous prostacyclin and steroids limited the development of gangrene [and subsequent amputation] toa single finger tip.

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.

In respect of follow-up, reviewing all ten 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 aspirin [to act as a platelet aggregation inhibitor] 75mg/day but refused 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, our most recent case, has autoamputated several digits and had a gangrenous heel removed surgically. Two of the patients have died - one of Covid and the other had a cerebral bleed while thrombocytopenic.

Discussion

Peripheral digital gangrene is a rare manifestation of SLE, being particularly unusual as a first presentation of the disease. [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%. The ten cases we report appear to fall into two groups, early [0-5 years] and late [20 years or more] post-diagnosis. In two patients in the early group, the gangrene was a presenting feature.

Although eight of our patients were diagnosed with SLE while an adolescent [age 12 – 20 years], 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 18.5 SD = 11.5 years 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 a combination of thrombotic and inflammatory disorders. APAbs are a likely background with other triggers factors including infection [present in 50% our of cases] and cryoglobulins [in two of our cases] being critical.

All the patients in our 'gangrene cohort' had active clinical and/or serological disease at the time the gangrene developed, which might imply an important role for disease activity in 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. Three of our t patients had an overlap of autoimmune diseases (Sjogren's, myositis autoimmune thyroid disease).

Because of the low prevalence of patients developing gangrene in the context of SLE, evidence for the optimal 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 whether intravenous 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 relief 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.

A commonly asked question by our patients is whether the gangrene can re-occur. From our data with very long-term follow up the answer is yes [two out of ten cases] but this is uncommon; the clear majority of these patients have not suffered a recurrence. 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 [14].

Patients whose SLE is complicated by gangrene are rare but it is a potentially devastating condition. Treatment must be initiated as soon as possible. Recurrence of the problem is uncommon 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	Case 9 20 years AAO Female; Black Caribbean	Case 10 20 years 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 [class IV] Arthritis Low platelet	Arthritis Extensive discoid lupu WHO II LN Sagittal sinus thrombosis DVT, stroke, PEs, stillbirth 24 weeks, Epilepsy	Arthritis Mucocutaneous [rash, mouth ulcers] Raynaud's
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	Positive dsDNA Low C3 Positive AntiRo, La, Sm and RNP APAb initially neg But in 2003: APS with stroke. B2GPI high IgG	Positive dsDNA Low C3 AP triple positive ENA negative AntiRNP positive ENA negative	ANA positive Anti-DNA positive Low C3 LAC positive Anti-Ro positive	ANA positive Anti-DNA positive Low C3 Anti-Sm positive LAC positive ACA positive [IgG}
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	Neutropenic sepsis Nephrectomy post-renal biopsy	Splenectomy for initial 'ITP' Superficial vein thrombosis x 2 Focal myositis Septic shock
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	32 years	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	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	Gangrene of left thumb, left thigh, all of her torso	Severe ischaemia of 3 finger tips; one became gangrenous
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	gangrene of 2nd – 5th fingers right hand, all fingers left hand; all fingers left foot; 4th and 5th toes right foot.	Auto amputation of index and middle finger	Partial right foot amputation	Combination of autoamputation and surgical debridement and removal of affected digits	Autoamputation of 1st finger left hand
Long term AC therapy/Other	Warfarin	?	Warfarin	Aspirin	Warfarin	Enoxaparin	Warfarin	Warfarin (including during second hit)	Enoxaparin	Rivaroxaban
Status	Alive	Deceased (COVID)	Alive	Alive	Deceased (Cardiorenal syndrome)	Alive	Alive	Deceased. Cerebral bleed linked to thrombocytpaenia.	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. APAb = antiphospholipid antibodies. APS = antiphospholipid antibody syndrome.

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.