CASE REPORT

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Case Report: Extensive digital gangrene as a primary manifestation of late-onset systemic lupus erythematosus

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Abstract

Background: Digital gangrene is a rare but serious complication of systemic lupus erythematosus (SLE). It occurs usually in middle-aged patients with longer disease duration.

Case: Herein we report the case of a 56-year-old man (with no history suggestive of Raynaud’s phenomenon, diabetes mellitus, smoking, trauma, infection, or chemical exposure), who presented with SLE and digital gangrene was among the first signs. He presented with a one-month history of joint pain, hair loss, photosensitivity, mouth ulcers, malar rash, dyspnea, and digital pain. Physical examination revealed painful and diffuse erythematous skin lesions in the extremities and back, as well as cyanosis in the fingers. We noted lymphocytopenia (600 cells/mm³), and an elevated C-reactive protein (15.1 mg/l) on laboratory tests. Immunological tests were positive for antinuclear antibodies (ANA) with Title 1:400. Pulmonary computed tomography revealed pulmonary fibrosis, and pulmonary function tests revealed the restrictive pulmonary disease. Diagnosis of SLE with lung involvement was retained. The immunological assessment in search of elements in favor of a vascular origin of the patient’s skin lesions was negative. Treatment was initiated with 200 mg/day hydroxychloroquine. For dermal and pulmonary involvement, intravenous (IV) pulse therapy was used with methylprednisolone (1,000 mg/d for three consecutive days monthly) and cyclophosphamide (1 g/month). Calcium blocking agents were also prescribed. However, the lesions did not improve. The patient was given two infusions of rituximab (1 g) at a 14-day interval with a marked improvement of the majority of vasculitis lesions, and a partial improvement of dyspnea.

Conclusions: Digital gangrene is a rare complication of late-onset SLE,
especially as a primary manifestation.

**Keywords**
Systemic lupus erythematosus, digital gangrene, vasculitis
Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organs and systems, characterized by an autoimmune response to nuclear antigens. Young women are most likely affected by this disease. This condition appears to be rare after the age of 50 years.1 With a cumulative incidence of 1.3%, digital gangrene is a rare but severe complication of SLE. It is the initial manifestation of the disease in only 0.2% of cases.2,3 It was initially identified by Dubois4 and Alarcon-Segovia.5 Mechanisms, such as vasculitis, thromboembolism, premature atherosclerosis, vasospasm, and coagulability can contribute to the development of gangrene.2 The major risk is digital amputation.2 Herein, we present a case involving a male patient with extensive digital gangrene as a primary manifestation of late-onset SLE associated with severe and necrotizing vasculitis in the absence of antiphospholipid antibody syndrome (PLAS), which was managed by rituximab.

Case report
This case involves a 56-year-old retired Caucasian male patient with a one-month history of joint pain, hair loss, photosensitivity, mouth ulcers, malar rash, dyspnea (New York Heart Association (NYHA) stage 3), and digital pain. Physical examination revealed good overall condition and normal vital signs. All peripheral pulses were palpable. Painful and diffuse erythematous skin lesions in the extremities and back, as well as cyanosis in the fingers were noted. Pulmonary auscultation showed small crackles. The rest of the physical examinations were normal. Based on these clinical manifestations, diagnosis of SLE was suspected. Laboratory examinations were therefore carried out and they revealed normal hemoglobin level (Hb=12.1 g/dl) (NV: >12 g/dl) and lymphocytopenia (600 cells/mm³) (NV: 3,000–9,500 cells/mm³). Platelets were normal at 209,000/mm³ (NV: >120,000/mm³). Partial Thromboplastin Time was at 83% (NV: >70%). The C-Reactive Protein was elevated (15.1 mg/l) (NV: <5 mg/l). Immunological tests were positive for Anti Nuclear Antibodies (ANA) with Title 1:400 (>1/160) speckled and anti-ds DNA dosed by ELISA (with a title of 102,37 UI/ml (NV: 50 UI/ml), anti-SSA 52, and anti-mitochondrial antibody M2. Anti-Smith, anti-SSB, anti-RNP antibodies, and Anti-Neutrophil Cytoplasmic Antibodies (ANCA) were negative. The test of serum Complements (CH50, C3, C4) was normal. Regarding digital pain, simple x-rays were performed and they did not show osteoarticular damage. Concerning dyspnea, pulmonary computed tomography (CT) revealed pulmonary fibrosis, and pulmonary function tests revealed restrictive pulmonary disease. Diagnosis of SLE with lung involvement was retained according to the American College of Rheumatology (ACR) classification criteria for SLE.6 Faced with cutaneous lesions suggestive of vasculitis, we re-examined the patient in search of thromboembolic risk factors. No history suggestive of Raynaud’s phenomenon, diabetes mellitus, smoking, trauma, infection, or chemical exposure was found. The patient had neither a personal nor a family history of thrombotic events. The immunological assessment in search of elements in favor of a vascular origin of the patient’s skin lesions was negative: Prothrombin, anti-Cardiolipin antibody (aCL), Lupus Anticoagulant (AL), antiß2 glycoprotein (GPI), and cryoglobulin levels were negative. Serological tests for hepatitis B and C and human immunodeficiency virus were also negative. The lipid profile was normal.

Treatment was initiated with 200 mg/day hydroxychloroquine. For dermal and pulmonary involvement, intravenous (IV) pulse therapy was used with methylprednisolone (PM) (1,000 mg/day for three consecutive days monthly) and cyclophosphamide (CTX) (1 g/month). Calcium blocking agents were also prescribed. A month later, the patient developed digital gangrene and the skin lesions increased (Figure 1) despite the treatment. Skin lesions were biopsied and the biopsy showed necrotizing vasculitis of SLE in the small vessels. Glucocorticoids (1 mg/kg/day) and anticoagulants (IV heparin infusion 600 UI/kg/day) associated with prostacyclin analog (iloprost, 0.1 mg IV) were therefore prescribed for four days. However, the lesions did not improve. The patient was given two infusions of rituximab (1 g) at a 14-day interval. Secondary infection of the skin lesions occurred and it was successfully treated with antibiotics, leading to a stabilization of digital gangrene, a marked improvement in the majority of vasculitis lesions (Figure 2), and partial improvement of dyspnea. Glucocorticoids were gradually reduced to 5 mg/day for three months.
The patient is currently being monitored on outpatient in the hand surgery department, he reports a marked improvement in skin lesions and dyspnea.

Figure 1. Skin involvement of the patient. A) Extensive digital gangrene. B) Skin necrosis of the thighs. C) Cutaneous substance loss around the left wrist. D) Cutaneous substance loss near the second metacarpophalangeal joint. E) Skin necrosis of the back.

Figure 2. Improvement of the skin involvement after rituximab infusion. A) Improvement of the back skin gangrene. B) Improvement of the digital gangrene. C) Improvement of the left wrist gangrene.

Patient perspective
The patient is currently being monitored on outpatient in the hand surgery department, he reports a marked improvement in skin lesions and dyspnea.
Discussion
To the best of the authors' knowledge, this is the first reported case of such extensive gangrene as a primary manifestation of late-onset SLE. Digital gangrene is a rare but severe complication of SLE, with a cumulative incidence of 1.3%. It is an inaugural manifestation in rare cases. Among 2,684 patients with SLE, digital gangrene occurred in 18 cases, corresponding to a frequency of 0.67% with an average age at the first occurrence of 33.1 years old and an average disease duration of 99.1 ± 60.1 months. It was furthermore stated by Rosato et al., that digital ulcers and gangrene are never found as the first presentation in SLE. However, some cases of digital gangrene as a primary event in SLE have been reported. The majority of cases reported in the literature have proved that digital gangrene occurs in young SLE patients and that the occurrence of this complication in older adult patients is extremely rare. To the best of the authors' knowledge, only three cases of digital gangrene have been reported in patients with SLE at an older age (after 50 years old). The first case was described by Vocks et al., in a 59-year-old female patient. The second was reported by Nagai et al., in a 50-year-old female patient followed for SLE since the age of 32 years with cutaneous, hematological, and neurological involvement. The third case was reported by Ha-Ou-Nou et al., in a 53-year-old male patient who presented with SLE manifested by extensive digital gangrene.

The pathophysiological mechanisms of digital gangrene in SLE are complex, involving thromboembolism, premature atherosclerosis, vasospasm, hypercoagulability, and vasculitis. Among these manifestations, anti-phospholipid syndrome is a significant risk factor. Jeffery et al., reported that positive antiphospholipid antibody syndrome is one of the causes of critical peripheral ischemia. Furthermore, in several reported cases, Doppler ultrasound or even arteriography have revealed digital artery occlusion or stenosis. In addition, biopsies have shown moderate and small-vessel vasculitis, even in the presence of normal Doppler ultrasound. In our patient, serological markers of antiphospholipid syndrome were negative, upper extremity CT angiography was normal, and skin biopsy showed vasculitis of a small vessel confirming its involvement in the occurrence of this complication. Other risk factors of gangrene have been advanced, including the long duration of the disease (four years), Raynaud’s phenomenon, and high serum CRP. The particularity in our patient is that he had no risk factors, and digital gangrene was one of the early signs of the disease. An other particularity of this case is the normality of the complement. This is not uncommon, since the complement may not be consumed in mostly a half of lupus patients. Indeed, in an European multinational inception cohort of 200 newly diagnosed SLE patients with active disease, low complement levels were observed at baseline in only 54%. Furthermore, Low complement levels are found even more infrequently in very early and milder disease.

The severity of this complication (gangrene) justifies the use of early high-dose corticosteroids associated with an immunosuppressive agent. Liu et al., reported that the risk of digital amputation declines after early high-dose corticosteroid treatment. Ziaee et al., reported a case of a 12-year-old girl treated for digital gangrene with corticosteroids and mycophenolate mofetil with a good outcome. Another case of SLE with digital gangrene was treated with corticosteroids and cyclophosphamide, with a significant improvement at the initial infusion. For associated anti-phospholipid syndrome, anticoagulation is mandatory. Vasodilators and vasoprotective agents should be prescribed in the case of Raynaud’s phenomenon. Immunomodulatory treatment, such as rituximab, has also been given to some patients after the failure of corticosteroids and immunosuppressants and it has shown good results. This was the case for our patient who did not respond to corticosteroid associated with cyclophosphamide. His lesions improved after two infusions of 1,000 mg rituximab at a 14-day interval. In advanced cases, surgery is necessary.

Conclusions
SLE with digital gangrene presenting as an initial symptom is rare, especially in late-onset SLE. Its pathophysiology is complex and multifactorial. Rituximab is a good treatment alternative in case of other treatments’ failure.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Consent
Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Authors contributions
Dr S B: Conceptualization, Writing- original draft, Supervision, Validation; Dr M B M: Data curation, Writing - original draft; Dr S R: Supervision, Validation; Dr S J: Data curation, Writing - original draft; Dr S R: Supervision, Validation; Dr K Z: Data curation, Writing - original draft; Dr H S: Supervision, Validation; Dr M E: Supervision, Validation.
References


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? Danieli Castro Oliveira de Andrade
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Well written case report of a rare manifestation of SLE: extensive vasculitis as presentation. Very important to have had evaluated antiphospholipid antibodies, that could have been easily missed, and cryoglobulinemia.

You need to provide the following additional information;
1. Did the patient smoke?

2. Can you please provide the SLE classification criteria that was used for diagnosis?

3. Can you give more details regarding anti-DNA: Was it done by ELISA, and Chritidia? Was it anti-ds DNA? What was the titer? This information is very important to add laboratorial specificity to your case, since anti-Sm was negative. It is very intriguing that complement was normal. You need to make a special consideration regarding it.

Is the background of the case's history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Yes

Is the case presented with sufficient detail to be useful for other practitioners? Yes
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Antiphospholipid Syndrome

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 01 Sep 2022

Soumaya Boussaid, La Rabta Hospital, La Rabta Jebbari, Tunis, Tunisia

Dear Reviewer,

thank you for your very insightful comments.

1. Did the patient smoke?
No, the patient did not smoke, we have insisted on this point in the following paragraph: "No history suggestive of Raynaud's phenomenon, diabetes mellitus, smoking, trauma, infection, or chemical exposure was found".

2. Can you please provide the SLE classification criteria that was used for diagnosis?

Yes, indeed we specified the SLE classification criteria in the following sentence "Diagnosis of SLE with lung involvement was retained according to the American College of Rheumatology (ACR) classification criteria for SLE. 6 "

1. Can you give more details regarding anti-DNA: Was it done by ELISA, and Chritidia? Was it anti-ds DNA? What was the titer? This information is very important to add laboratorial specificity to your case, since anti-Sm was negative. It is very intriguing that complement was normal. You need to make a special consideration regarding it.

You are right, it is important to mention all the data you quoted. in light of your recommendations, we have addeted all information as follow: "Immunological tests were positive for Anti Nuclear Antibodies (ANA) with Title 1:400 (>1/160) speckled and anti-ds DNA dosed by ELISA (with a title of 102,37 UI/ml (NV: 50 UI/ml), anti-SSA 52, and anti-mitochondrial antibody M2. Anti-Smith, anti-SSB, anti-RNP antibodies, and Anti-Neutrophil Cytoplasmic Antibodies (ANCA) were negative."

For complement normality, we added a paragraph in the discussion section as follows: ". An other particularity of this case is the normality of the complement. this is not uncommon, since the complement may not be consumed in mostly a half of lupus patients 17. Indeed, in an European multinational inception cohort of 200 newly diagnosed SLE patients with active disease, low complement levels were observed at baseline in only 54% 17. Furthermore, Low complement levels are found even more infrequently in very early and milder disease18."

Competing Interests: we declare that we have no competing of interest
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