An Unusual Case of Late-onset Systemic Lupus Erythematosus Presenting with Digital Gangrene

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ABSTRACT

Digital gangrene is an uncommon initial manifestation of systemic lupus erythematosus (SLE) and rarely in late-onset disease. This case presents a 50-year-old woman who developed digital gangrene and was subsequently diagnosed with SLE. Early treatment with immunosuppression and anticoagulation halted the progression of the digital ischemia. This case highlights that late-onset SLE, often described as having a more benign and insidious course, can also present with catastrophic limb-threatening manifestations.

Keywords: Late-onset, digital ischemia, lupus

INTRODUCTION

As the prototypical chronic autoimmune disease characterized by multisystemic involvement, systemic lupus erythematosus (SLE) has been established to predominantly affect individuals during their reproductive years.[1] A small subpopulation of SLE has been described in which the disease occurs after the age of 50, with differing results on sex ratio across studies. Late-onset SLE has been characterized by a more benign and insidious course in most current literature.[2,3] Furthermore, compared with adult-onset SLE (ages ≥18 and <50), late-onset SLE has a lower number of American College of Rheumatology (ACR) criteria fulfilled and lower disease activity.[4]

The risk of developing a thrombotic event in SLE is higher than in the general population. This risk increases further when associated with other factors or in the presence of inherited or acquired pro-thrombotic abnormalities or trigger events. Digital gangrene as a severe complication of thrombosis in SLE is rare and is seen mainly at a late stage of the disease proposing that a long history of SLE is considered a risk factor.[5] Even rarer is the incidence of digital gangrene as an initial manifestation of SLE.[6] Currently, there are only a few published articles on digital gangrene as an initial manifestation of SLE, and these studies include patients in the younger age group. To our knowledge, this is the first report in the country of a late-onset SLE patient who presented with digital gangrene.

CASE PRESENTATION

A 50-year-old Filipino female, nulligravid, current smoker, with no known comorbidities, was seen at the Emergency Department for a 1-day history of sudden pain

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and black discoloration of toes. On further interrogation, she reported having experienced a 5-month history of intermittent pain with paresthesia on both feet extending to the legs, worse during afternoons and evenings. She was partially relieved when soaked in warm water.

The patient arrived at the emergency room dyspneic at rest with a rate of 26 breaths per minute, elevated blood pressure of 150/100 mmHg, a heart rate of 100 beats/minute, and a temperature of 37 degrees Celsius. She complained of severe pain on both feet extending to the legs. Physical findings showed dry gangrene of the 1st and 2nd toe on the right, 2nd toe on the left, accompanying non-pitting edema, tenderness, warmth, and erythema on adjacent skin (Figure 1). All the peripheral pulses were normal.

There were ecchymoses on the 2nd digit of the right hand, posterior surface of the left arm, and lateral aspect of the right thigh. Moreover, there were no alopecia and oral ulcers, livedo reticularis, Raynaud's phenomenon, arthritis, or nail changes. Multiple well-demarcated erythematous papules and plaques were noted on the eyebrows, cheeks, nose, and chin with sparing of the nasolabial creases. Biopsy of the rash revealed perivascular and periadnexal lymphocytic infiltrate in the epidermis and dermis consistent with cutaneous lupus erythematosus (Figure 2). Unfortunately, a biopsy of the cutaneous ulcers was not performed.

On initial workup, there was serositis evidenced by pleural effusion on chest radiograph, anemia with leukocytosis and neutrophilia, as well as a +2 to +3 proteinuria on the dipstick. Further workup on the anemia revealed its hemolytic nature and a positive direct Coomb's test. The proteinuria was subsequently quantified using 24-hour urine determination, which yielded 11.71 grams. Additional evidence of nephritis included dysmorphic urine red blood cells (52%). Doppler Ultrasonography of both lower limbs showed extensive deep vein thromboses and atherosclerosis plaques with no significant luminal stenosis. Abdominopelvic CT scan showed bilateral renal vein and femoral vein thromboses.

Due to her smoking status, thromboangiitis obliterans and atherosclerotic arterial disease were also considered. However, multisystemic involvement prompted a more thorough search for an underlying condition. Her autoimmune workup revealed a positive antinuclear antigen (ANA) titer of 1:100 with +4 speckled pattern, positive p-antinuclear cytoplasmic antibody (p-ANCA), an elevated activated partial thromboplastin time (aPTT), lupus anticoagulant, and direct Russel Venom Viper test (DRVVT). However, she tested negative for anti-double-stranded DNA (anti-dsDNA).

She was managed with Methylprednisolone pulse therapy for three days, followed by cyclophosphamide for nephritis and low-molecular-weight heparin (LMWH) and aspirin for the thromboses. On subsequent monthly follow-up, economic constraints hindered confirmation of the antiphospholipid (APL) antibodies, but digital ulcers were wholly resolved (Figure 3) with no evidence of recurrence.

DISCUSSION

SLE is a chronic autoimmune disease of unknown cause, characterized by the production of autoantibodies against a variety of nuclear antigens, the involvement of multiple organs, and a broad spectrum of clinical manifestations. It is possible that more than one process could contribute to the disease and that different processes may be responsible for other disease manifestations.[7]

Although it usually affects women of reproductive age, available literature has described disease onset at 50 years and older. This cohort is referred to as having late-onset SLE and was described as having a more benign course, with less major organ involvement. The overall proportion across different studies of late-onset SLE is relatively low, ranging from 4% to 20%.[8]

A meta-analysis including 1,727 late-onset SLE patients showed that overall, cutaneous manifestations are less common in late-onset SLE patients, except for sicca symptoms.[9]

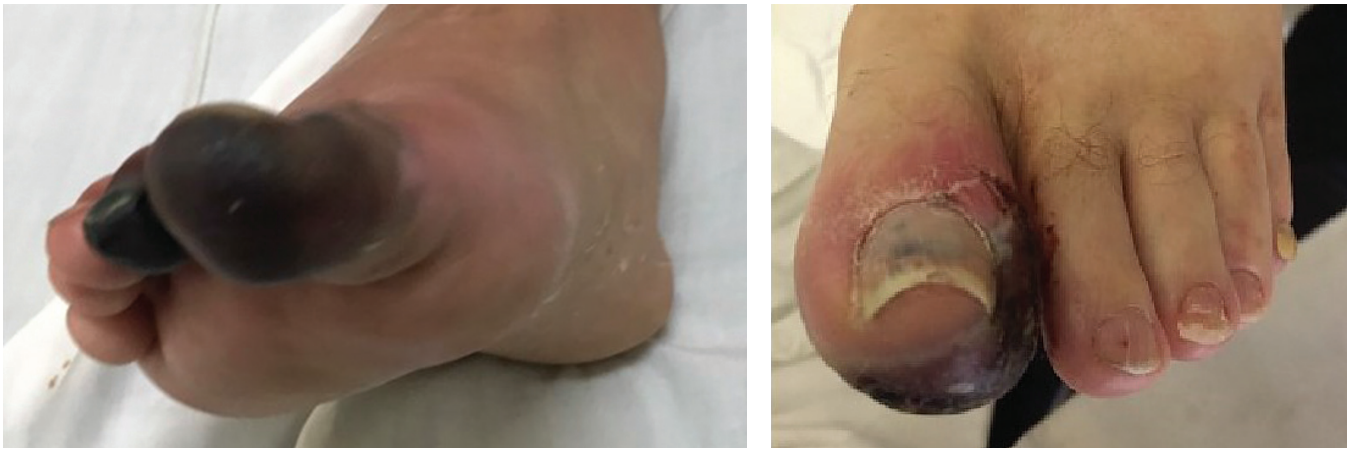

Figure 1. Dark violaceous discoloration of bilateral toes on initial presentation.

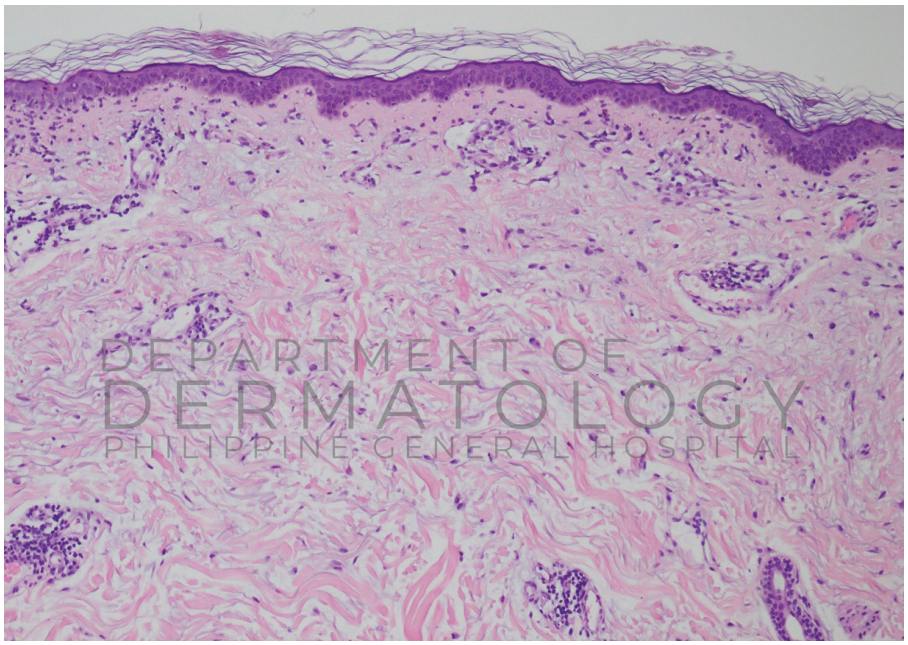

Figure 2. Low power view (H&E staining): skin punch biopsy consistent with cutaneous lupus showing basketweave orthokeratosis, atrophic epidermis with flattened rete ridges, and perivascular and periadnexal lymphocytic infiltrates in the superficial to mid dermis.

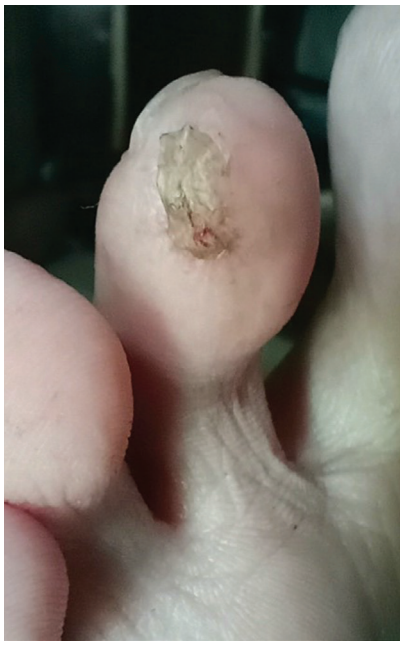

Figure 3. Healed ulcer on right toe on follow-up.

Our patient presented with multiple thromboses causing digital and cutaneous gangrene and venous thromboses in the viscera, which most likely contributed to the renal insufficiency. Digital gangrene was regarded as a rare initial presentation of SLE.[10] Dubois initially reported a 1.3% prevalence. Very few reports have been published since then, and the majority described the incidence on women of reproductive age. In China in 2009, of 2,684 SLE patients screened, only 18 patients had evidence of digital gangrene. All of them are in their reproductive age (33 ± 11 years old).[11]

Our case highlights not only the rarity of digital gangrene as an initial manifestation of SLE but also underscores its occurrence in late-onset SLE. A similar case of late-onset SLE was reported in France in 2016, describing a 53-year-old man who presented with painful cyanosis of upper extremities.[12]

Our patient presented with a positive p-ANCA which raised the question of whether ANCA is contributory to the pathogenesis of or has an association with SLE.[13] Su, et al., reported that ANCA was positively associated with SLE disease activity and might be used to differentiate lupus nephritis from SLE without nephritis. Another study demonstrated that among patients with new-onset lupus, those with positive ANCA (p- ANCA) significantly correlated with SLE disease activity and exhibited a higher incidence of lupus nephritis.[14] Further specifications of antibodies against MPO and PR3 could be done.

Another factor contributing to the digital gangrene in our patient is the possibility of APS. In itself, APS uncommonly presents with digital gangrene – only 3.3 to 7.5% of all APS patients.[15] Although our patient did not have the classic presentation of APS such as livedo reticularis and recurrent ulcers, APS is still a consideration given the initial positive lupus anticoagulant and presence of multiple thromboses. With that in mind, the condition of Catastrophic antiphospholipid syndrome (CAPS) has been considered. The multiple vascular thromboses in CAPS, as described by Miyakis, et al., are seen in our patient, but further workups were not done due to economic constraints.[16] Nevertheless, the ulcers likely represent a complication of both vascular thrombosis and vasculitis from SLE due to the presence of thrombosis in other sites and the high SLE disease activity.

There are various approaches in treating SLE with multiple or recurrent thromboses. Still, they generally require aggressive anticoagulation paired with control of disease activity to prevent recurrence of future thrombotic events. Patients with definite APS with or without SLE who have experienced a venous thrombotic event are recommended to use warfarin with a target INR of 2.0 to 3.0. However, in patients with definite APS and SLE with recurrent venous thromboembolism or arterial thrombosis, some literature recommends treating with warfarin to target an INR of 3.0 to 4.0.[15] The anti-malarial drug, hydroxychloroquine, one of the mainstay therapies for SLE, also has anti-thrombotic effects. Studies have shown that patients taking hydroxychloroquine have a lower risk of vascular events.[17]

Most patients given early active treatment pull through without complications, but secondary infection of gangrene

sites and amputation have been reported even with aggressive treatment.[11] Our patient was started with anticoagulation with warfarin, aspirin, corticosteroids, and cyclophosphamide as immunosuppression. On follow-up, there was a significant clearance of cutaneous and digital ulcerations.

CONCLUSION

This case highlighted that late-onset SLE, often described as having a more benign and insidious course, can also present with catastrophic manifestations such as limb-threatening digital ischemia. This may be from vascular thrombosis or a complication of vasculitis from SLE. Using available data on treatment, we have successfully initiated anticoagulation, corticosteroids, and immunosuppressants, which resulted in the resolution of ischemia and healing of cutaneous ulcers. Among patients who present with digital gangrene, SLE should be considered as an essential differential diagnosis regardless of the age of onset. Early aggressive management is vital to prevent life and limb-threatening complications.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

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