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Digital Gangrene: A Rare Cutaneous Manifestation of Systemic Lupus Erythematosus in The Absence of Anti-Phospholipid Antibodies

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ABSTRACT

Distal gangrene is a rare and serious manifestation of systemic lupus (LS). Secondary to vasculitis, this complication is most frequently associated with the presence of antipospholipid antibodies. Gangrene affecting all four extremities at the same time is exceptional in addition in the absence of antiphospholide antibodies. We report the observation of a 52-year-old patient with an LS for 16 years, who presented for necrosis of the four extremities of simultaneous installation evolving for 01 month. In addition to the noted dry gangrene, she had peripheral sensorimotor neuropathy in the lower extremities. Despite general corticosteroid therapy, its management required amputation of the fingers and forefeet. We also propose a review of the literature with an analysis of the cases reported to date, i.e. 85 cases including our observation.

Keywords: *Lupus, Digital Necrosis, Gangrene, Vasculitis, Peripheral Neuropathy*

Introduction

Systemic lupus (LS) is a complex autoimmune disease with variable clinical features (Rahman and Isenberg, 2008). Among its manifestations, skin lesions are the most common clinical signs (Cervera *et al*., 2003). The best known are: malar erythema, photosensitivity, alopecia, discoid lupus lesions, and various signs of cutaneous vasculitis, such as urticarial vasculitis, livedo, Raynaud's phenomenon and digital necrosis (Ribero *et al*., 2017). The latter is considered a very rare condition, it concerns less than 1.3 % of patients (Tuffanelli and Dubois, 1964; Jeffery *et al*., 2008; Liu *et al*., 2009). The incriminated mechanism in this damage would be poor tissue perfusion caused either by vasculitis, vasospasm, thromboembolism or accelerated atherosclerosis (Jeffery *et al*., 2008; Liu *et al*., 2009). Moreover, Antiphospholipid antibodies

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have been recognized as influential factors in the progression of atherosclerosis in addition to increased susceptibility to thrombosis. Indeed, Previous studies have revealed a higher prevalence of Antiphospholipid antibody positivity among patients with gangrene (Jeffery *et al*., 2008). The distribution of these lesions is variable. Nevertheless, involvement of all four extremities is the least described in the literature (Liu *et al*., 2009). The consequences of this gangrene are most often serious, going as far as amputation (Jeffery *et al*., 2008). We report the case of a lupus patient who presented simultaneous fingers and toes necrosis after a long history of Raynaud's phenomenon without antiphospholipid syndrome.

Observation

A 52-year-old patient, with well controlled hypertension on Irbesartan 300 mg/d, followed for 16 years for cutaneous-articular lupus, diagnosed according to the criteria of the American college of rheumatology ACR 1997 (Hochberg, 1997). She had bilateral and symmetrical distal polyarthritis, malar erythema, photosensitivity with anti-nuclear antibodies (ANA) positive at 1/640 (Norms <1/80) homogeneous without specific target. She did not smoke and had no family history of thromboembolic events. Follow-up was irregular due to the patient's lack of discipline with non-adherence to hydroxychloroquine. the last five years have been marked by the appearance of a phenomenon of Raynaud in its syncopal form treated with diltiazem 60 mg/d that the patient stopped taking after 3 months.

The patient presented to the internal medicine department for management of necrosis of the four extremities, which was bilateral and symmetrical, of simultaneous installation, and evolving for approximately one month.

Clinical examination on admission found dry gangrene involving the extremities bilaterally and symmetrically. In the upper limbs the necrosis concerned the last phalanges, surrounded by an inflammatory border, it spared the thumbs and the two middle fingers (Fig. 1).

Figure 1: Digital necrosis.

There was also a flame-shaped subungual hemorrhages on the left thumb (Fig. 2) with reticulate erythema on the right thumb (Fig. 3).

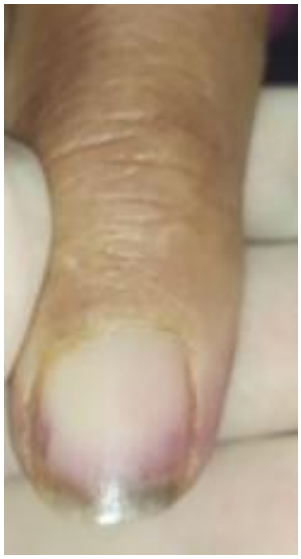

Figure 2: Subungual hemorrhages.

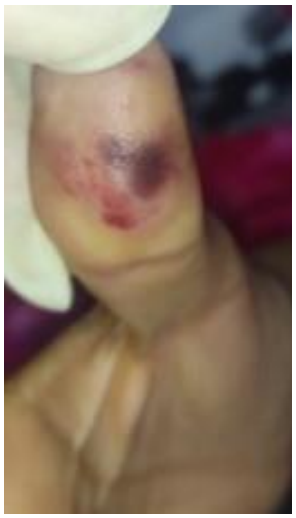

Figure 3: Reticulate erythema.

In the lower limbs the necrosis affected all the toes, also limited by an inflammatory border (Fig. 4).

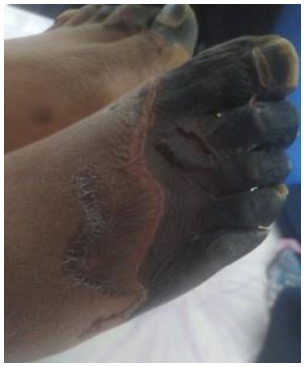

Figure 4: Toe necrosis.

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Two other necrotic lesions were present next to the Achilles tendons. All arterial pulses were present and symmetrical. Neurological examination revealed a stepping gait with loss of tactile and thermo-algesic sensitivity in the legs.

In biology, there was a bi-cytopenia; lymphopenia at 900/mm^3 and non-regenerative hypochromic microcytic anemia at 7.1 g/dl of hemoglobin with a negative direct Coombs test. A chronic inflammatory reaction on serum protein electrophoresis (PEP), an erythrocyte sedimentation rate (ESR) at 120 mm the 1st hour and a C-reactive protein at 17 mg/l. Viral serologies (HIV1-2, hepatitis B, hepatitis C, Sars-cov2) were negative. The rest of the biological assessment (glycemia, creatinine, blood ionogram, Coagulation tests, transaminases) was without abnormalities.

Immunologically, absence of cryoglubulinemia in serum, anti-nuclear antibodies (ANA) were positive at 1/1000 with homogeneous and speckled (HS) pattern, native anti-DNA and anti-nucleosomes were positive, absence of anti-phospholipid antibodies and circulating lupus anticoagulant.

The standard X-ray did not show any osteoarticular involvement. Arterial and venous Doppler ultrasound of the upper and lower limbs was without abnormalities.

The electrocardiogram showed regular sinus rhythm and echocardiography was normal.

The spinal MRI was without abnormalities, no demyelinating or inflammatory lesions were found. Electroneuromyogram (ENMG) of the lower limbs showed severe diffuse peripheral neurogenic sensory-motor axonal damage.

Histologically, biopsies of reticular erythema showed a perivascular inflammatory infiltrate made up of lymphocytes and polymorphonuclear neutrophils (PNN), with a hyperkeratotic acanthotic epithelium and a dermis remodelled by fibrosis.

Regarding the treatment, we introduced boluses of 500 mg of methylprednisone for 3 successive days with oral relay with prednisone at 1 mg/kg/d in addition of initial anticoagulation of 2 weeks that was stopped after confirming the absence of anti-phospholipid antibodies. For peripheral neuropathy treatment 3 courses of immunoglobulins at 2 g/Kg/d were administered. Hydroxychloroquine 400 mg/d, diltiazem 60 mg/d, Bosentan 6.25 mg/d and azathioprine at 2 mg/kg/d were associated with this treatment.

The evolution was marked after the corticosteroids with a stabilization of the inflammatory lesions. A few days later, an amputation of the necrotic extremities was performed.

Methods

A search on Google scholar and Pubmed for articles that were published between 1911 and February 2022 in English, containing the following MeSH (Medical subject headings): lupus and gangrene, vasculitis. We only retained articles dealing with peripheral gangrene in adults and children. Data analysis was performed using SPSS software version 26.0 (IBM).

Discussion

The observation of our patient presents several characteristics, in addition to gangrenous involvement which is a rare manifestation of systemic lupus, her particular clinical presentation with a symmetrical distribution affecting the four extremities at the same time and their simultaneous installation. This gangrenous occurred on an authentic lupus disease without the presence of anti-phospholipid antibodies. This rare association was first reported by Dawson in 1911 in a 49-year-old man (Dawson, 1911).

Later, in 1962 Dubois, *et al.* described five cases of digital gangrene in lupus patients (Dubois and Arterberry, 1962). Other studies confirmed the rare nature of this association with a prevalence ranging from 0.7 % to 6 % of lupus patients depending on the series (Jeffery *et al*., 2008; Liu *et al*., 2009; Rajasekhar *et al*., 2009). The most important of them, the one having collected 2684 cases of LS where only 18 patients presented digital necrosis (Liu *et al*., 2009).

To date, including our observation, only 85 cases of peripheral gangrene associated with lupus have been published in the literature (table=27 articles). These are 79 adults and 6 children with a female predominance (sex-ratio F/M: 6.4). The average age of these patients at the onset of gangrene was 35.04 ± 14.6 years, with an average time to onset from the diagnosis of lupus of 80.45 ± 60 months. Prolonged duration of disease progression is, according to Liu, *et al.* (2009) a predictive factor of this association. Nevertheless, in some cases, gangrene can be the revealing manifestation of lupus (Jeffery *et al*., 2008; Whiting, 1967; Cheah, 1973; Jindal *et al*., 1983; Asherson *et al*., 2007). This damage can be associated with other cutaneous manifestations such as photosensitivity and cutaneous vasculitis. Its seat and its extent are variable, it can be limited or touch the 4 extremities. Indeed, the gangrene involved the 4 limbs in 25.5 % of the cases (12 observations/47), and it was symmetrical in 31 patients either at the level of the hands or the feet (65.95 %). The associated factors were Raynaud's phenomenon in one out of two cases (56.45 %), the notion of cutaneous vasculitis in 43.5 %, smoking in 22 %, sepsis in 14 %, hypertension in 13 %, and finally diabetes in 3 %. Involvement of medium caliber vessels was noted in 22.35 % of cases. Only Igaki reported an association with calciphylaxis (Igaki *et al*., 2001).

Biologically, a high CRP is observed in one out of three observations (21/65 cases). As for immunological disturbances, anti-DNA were present in 72 % of cases, APL in 45.61 %, one case of cryoglubulinemia (Whiting, 1967) and another of constitutional thrombophilia (Yasmin *et al*., 2020).

This clinico-biological disparity presented by the gangrene associated with lupus disease testifies to the diversity of the pathophysiological mechanisms involved. Indeed, the occurrence of digital gangrene during SLE could be the result of vasculitis, thromboembolism especially linked to the presence of anti-phospholipid antibodies, and early atherosclerosis whose origin is multifactorial (Liu *et al*., 2009). Vasculitis is probably the major mechanism. The anatomopathological study of the lesions in our patient and most of the reported observations revealed vasculitis of medium and small caliber vessels (Liu *et al*., 2009). In our case, we did not find anti-phospholipid antibodies or cryoglubulinemia.

On the therapeutic level, no specific therapeutic strategy is codified.

Almost all (91 %) of the patients received corticosteroid therapy (Jeffery *et al*., 2008; Liu *et al*., 2009; Dubois and Arterberry, 1962; Rajasekhar *et al*., 2009; Cheah, 1973; Jindal *et al*., 1983; Igaki *et al*., 2001; Alzughayyar *et al*., 2020), the associated treatment was variable depending on the series comprising an immunosuppressant (Jeffery *et al*., 2008; Liu *et al*., 2009; Rajasekhar *et al*., 2009; Vocks *et al*., 2000; Adelowo *et al*., 2012; Kurnia *et al*., 2012; Alghamdi, 2015; Vijay *et al*., 2017; Alzughayyar *et al*., 2020; Ha-Ou-Nou *et al*., 2017) prostaglandin (Jeffery *et al*., 2008; Liu *et al*., 2009; Rajasekhar *et al*., 2009; Igaki *et al*., 2001; Omair *et al*., 2012; Alghamdi, 2015), epoprostenol (Jeffery *et al*., 2008), anticoagulation (Jeffery *et al*., 2008; Yasmin *et al*., 2020; Vocks *et al*., 2000; Nagai *et al*., 2009; Adelowo *et al*., 2012; Kurnia *et al*., 2012; Alzughayyar *et al*., 2020; Ha-Ou-Nou *et al*., 2017) rituximab (Ribero *et al*., 2017; Jeffery *et al*., 2008; Sonkar *et al*., 2019; Alalawi *et al*., 2020), thrombolysis (Ando *et al*., 2020), plasmapheresis (Lee *et al*., 2010) and intravenous immunoglobulins (Alzughayyar *et al*., 2020). Despite this treatment, amputation was necessary in the majority of cases (2/3). Is this recourse to amputation linked to the ineffectiveness of the treatment itself or to its late initiation?

According to the study by Liu, *et al.* (2009) on 18 patients, the initiation of corticosteroid therapy within 3 weeks of the onset of necrosis significantly reduced the risk of amputation (Liu *et al*., 2009). The severity of this cutaneous involvement does not only affect the functional prognosis but also, in certain cases, the vital prognosis of the patient, which implies early management combining high-dose corticosteroid therapy and an immunosuppressant (Liu *et al*., 2009; Vocks *et al*., 2000; Ha-Ou-Nou *et al*., 2017). Anticoagulation only has a place in the event of an associated anti-phospholipid syndrome (Liu *et al*., 2009).

Conclusion

Digital necrosis in lupus is a rare and serious skin condition. Its pathophysiology is multifactorial. Its appearance is favoured by the duration of evolution of lupus disease, the presence of Raynaud's phenomenon and the importance of the inflammatory syndrome. Despite the absence of a standardized therapeutic approach, its management must be early to limit the sequelae and avoid amputation.

Contributions: Lamia Bengherbia, Taharboucht said: writing the paper, concept and design, and data collection. Oussama Souas, Nadia Touati, Hassina Chicha, Ahcene Chibane: data collection, data interpretation

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