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Neurological manifestations in systemic lupus erythematosus: A case with an individualized therapeutic approach

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ABSTRACT

Vasculitis occurs frequently in systemic lupus erythematosus (SLE) patients with an active disease and poor prognosis. Nervous system vasculitis – specifically, multiple mononeuropathy, seizures, and transverse myelitis – is among the most severe complications in SLE that need timely aggressive therapy. Unfortunately, no robust literature is available to guide their management, and therapeutic recommendations are commonly based on other autoimmune conditions or case reports, case series, and expert opinions. We hereby present a case of a 27-year-old female patient with SLE that sequentially developed an asymmetric distal axonal sensorimotor neuropathy in her limbs and digital ischemic lesions of the hands, that progressed despite maximal treatment with standard therapies, thus requiring several sessions of plasmapheresis.

Keywords: lupus vasculitis, antiphospholipid syndrome, plasma exchange

INTRODUCTION

Lupus vasculitis (LV) is one of the secondary vasculitides occurring in the setting of systemic lupus erythematosus (SLE) in approximately 50% of patients [1]. Involvement of the peripheral nervous system (PNS) is less frequently observed than central nervous system (CNS) involvement, occurring in less than 10% of patients with SLE, although electrophysiological studies may be abnormal in up to 23% of cases [2,3]. Among autoantibodies, anti-endothelial cell antibodies (AECA) are the main cause of endothelial damage [4]. Other types of autoantibodies that may be involved in the pathogenesis of lupus vasculitis (LV) are antineutrophil cytoplasmic antibodies (ANCA), anti-phospholipids antibodies (aPL), and anti-double strain DNA (Anti-dsDNA) [5]. Vascular injury and antiphospholipid syndrome (APS) are often present simultaneously in SLE patients and are closely interconnected given that aPL can contribute to the damage of vascular endothelium during the vasculitic process [6].

Over the past few decades, plasma exchange was extensively used in SLE, and some published data suggested that they may be successfully used as an adjunctive therapy. However, their efficacy has only been reported in retrospective studies. Indeed, when tested prospectively, no benefit was clearly demonstrated [7].

CASE REPORT

A 27-year-old white woman with no prior medical history, was admitted to our hospital in October 2021 with high fever, diffuse arthralgia, progressive weakness in her lower limbs with unsteady gait and concomitant bilateral digital necrosis, 6 weeks before, she had applied to another clinic with complaints of joint pain and swelling in the hands and feet. She was first diagnosed with rheumatoid arthritis and she was treated with methotrexate and a high-dose short-course oral steroid taper. One month after, she subsequently developed multi-digit acrocyanosis [Figure1(a)] and worsening numb-

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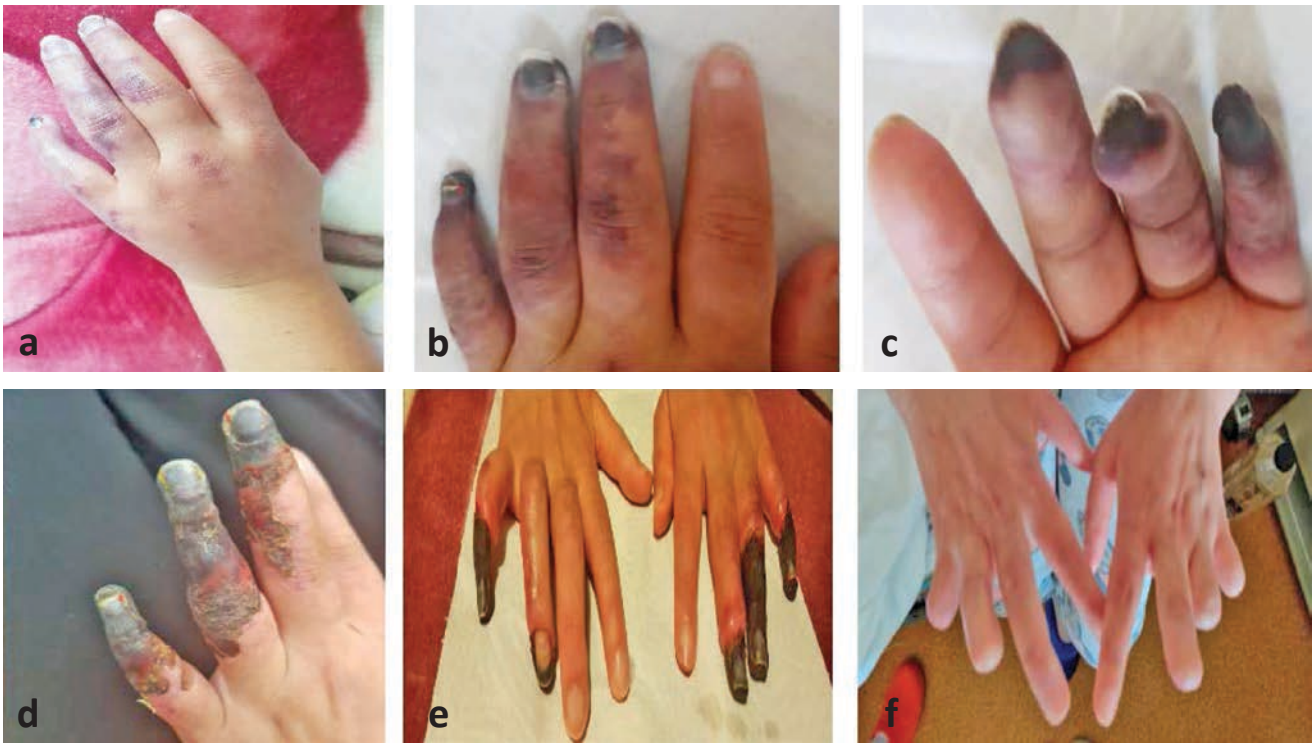

FIGURE 1. (a) Left hand edema and acrocyanosis (before treatment). (b),(c) Bluish discoloration of the left 3rd to 5th digits with gangrenous skin changes which involved the distal and middle phalanges (on admission).(d) Digital necrosis of the left 3rd to 5th digits with gangrenous skin changes (2 weeks after initial treatment with cyclophosphamide). (e) As the disease activity decreased, the digital necrosis began to be defined and a skin of demarcation line was noted at this level, after plasmapheresis therapy. (f) Amputation proximal to the interphalangeal joints bilaterally (6 months from onset of the disease)

ness and burning in her feet. Further blood tests revealed elevated acute phase reactants [C-reactive protein: 164.62 mg/L (normal: 0-5 mg/L), erythrocyte sedimentation rate (ESR): 99 mm/hr (normal: 0-15 mm/hr)], moderate anemia (hemoglobin: 9 g/ dl), lymphopenia (0.76 × 103/L) and hypocomplementemia [serum C3 42.6 mg/dl (normal: 90-180 mg/dl), serum C4 2,6 mg/dl (normal: 10-40 mg/dl)]. The immune profile reported: elevated Anti-dsDNA antibody titers (>200UI/ml), weakly positive anti-RNP/Sm, anti-nucleosome, anti-ribosomal P (anti-Rib-P) and anti-histone antibodies, high levels of IgM anticardiolipin antibodies (>90 UI/ml); positive direct Coombs and VDRL tests results; negative TPHA, negative CCP antibodies and negative rheumatoid factor. She was diagnosed with SLE with musculoskeletal, hematological and nervous system involvement, and also with secondary APS and she received oral corticosteroids, Hydroxicloroquine and baby aspirine.

The clinical picture was complicated after discharge with paraparesis and rapidly progressive digital ischemia, therefore the patient was urgently referred to our rheumatology department. On the admission day in our clinic the patient was acutely ill looking, febrile (39.8°C). She was normotensive (BP 100/50 mmHg) and her pulse rate was 120/minute. Livedo reticularis was distributed along the lower extremities. There was bluish discoloration of the right 4^{th}-5^{th} digits as well as left 3^{rd} and 5^{th} digits [Figure 1 (b, c)] with gangrenous skin changes which involved the distal and middle phalanges; asymmetric distal leg weakness and a severe sensory loss were noticed.

Laboratory findings were as follows: WBC: 16.25 × 10^3/L, Hb: 9.8 g/dL, platelet count 379 × 10^3/L; ESR:99 mm/hr, CRP: 153.27 mg/L, D-dimer levels slight elevated 1103 FEU/ml (normal <550 FEU/ml); microscopic hematuria and trace proteinuria on urinalysis, proteinuria 259.2 mg/24 h. Peripheral blood smear indicated slightly hypochromic red blood cells, arranged in rolls, hyper granulated neutrophil granulocytes and large, vacuolar monocytes. Immunologic studies revealed higher levels of ds-DNA antibodies [117,8UI/ml (negative <15 UI/ml)] and a triple positive antiphospholipid antibody profile. There was hypocomplementemia with a C3 level of 56 mg/dl and a C4 level of 36 mg/dl, respectively. The cryoglobulins test was negative. Infectious investigations were performed returning negative.

Subsequent neurological consultation confirmed the motor and sensory deficits. Her cranial magnetic resonance (MRI) angiography was unremarkable, and the spine MRI (thoracic and lumbar) did not highlight pathological contrast outlets at the level of the medullary cord, dura, nerves, vertebral and paravertebral bodies. Consequently, we decided to perform an electromyography that revealed severe subacute axonal sensorimotor polyneuropathy compatible with the

suspicion of mononeuritis multiplex. A visual field analysis revealed arcuate defects bilaterally in the superior and inferior nasal parts of the optic nerve, suggestive of bilateral optic neuritis. Doppler ultrasound of both upper and lower limbs was reported as normal. The cardiac ultrasound showed no signs of endocarditis and computed tomography of the chest, abdomen, and pelvis showed small liquid pericarditis, multiple axillary and retroperitoneal lymph nodes of a maximum of 18/13 mm.

Although she received intravenous (IV) maximal medical therapy: corticosteroids (0.5–1 g daily for 5 days), cyclophosphamide (CYC) pulses (500mg at 2 weeks apart), and prostaglandin (Alprostadil,2 mcg/kg/min), her condition continued to deteriorate. She complaint of headache, dizziness and nausea. High fever spikes persisted, increasing in frequency. Because of rapid progression of severe asymmetric muscle weakness involving legs and arms, and worsening of digital ischemia with gangrenous changes in multiple fingers (Figure 1-d), at day 8 of the hospitalization, it was decided to perform plasmapheresis (every other day for five sessions). The neurological evaluation performed after the 4th plasma exchange session, revealed a modest improvement, with regression of motor deficit in all limbs at MRC grade 3/5, and a marked recovery in her sensory function. We decided to continue kinetotherapy and the supportive treatment with further favorable evolution, and she was discharged three weeks after admission. In the presence of aPL, the patient was first anticoagulated with low molecular weight heparin (LMWH) before long-term treatment with acenocumarol. Methylprednisolone was continued in a dosage of 0.5 mg/kg and she also received IV monthly pulses CYC for 6 months (cumulative dose 3 g). In an attempt to reduce the dosage of CYC, she was given Mycophenolate mofetil (MMF) in a dosage of 2 g/day, as some studies have reported beneficial effects of MMF in the treatment of severe lupus vasculitis. As the disease activity decreased, the digital necrosis began to be defined and a skin of demarcation line was noted at this level [Figure1(e)]. In order to improve patient's quality of life, 6 months from onset of the disease, in conditions of low disease activity, it was decided to perform an amputation proximal to the interphalangeal joints bilaterally [Figure 1(f)].

During 12 months of follow-up, she remained with asymmetric hand weakness, right hallucis and index paresis, and patchy sensation loss of the right hand. In the lower extremities, she had a near-normal muscle strength (graded 4/5 MRC – scale). Sensation was decreased to pinprick in his left limb to the midcalf and decreased to vibration and proprioception at the 4 and 5 toes bilaterally. The optic nerve swelling had decreased and her vision had returned to normal. Investigations revealed positive antinuclear antibody (ds-DNA antibodies 43UI/ml) and hypocomplementemia(C3 72.61 mg/dL).

DISCUSSION

This case is presented to highlight an unusual presentation of SLE that presented with rapid progression of severe asymmetric muscle weakness and worsening of digital ischemia with gangrenous changes in multiple fingers, as their initial presentation in the hospital. Remarkably was the fact that she had a favorable response to therapeutic plasmapheresis after a failed trial of high dose IV methylprednisolone and CYC.

Significant clinical heterogeneity exists in profile of patients with SLE – related APS. Treatment depends upon the organs involved and the severity of the vasculitis process. In SLE, 30%-40% of patients are positive for aPL, whereas the prevalence of a clinically significant aPL profile in lupus patients is approximately 20% [8].

Vasculitic neuropathy associated with SLE has a characteristic clinical presentation with progressive sensorimotor symptoms developing over weeks to months [9]. Our patient had early complex and unusual manifestations requiring aggressive immuno-ssuppresion and had a pronounced response to therapeutic plasmapheresis. The constitutional symptoms, such as intermittent fever, asthenia, arthritis and involuntary weight loss, presence of livedo reticularis and digital ischemic lesion of the hands suggested an underlying systemic vasculitis and provided clues to the etiological diagnosis. Mononeuritis multiplex development has been rarely associated with antiphospholipid antibodies; as far as we know, there are only three cases reported [10-12]. This has not been clearly associated with diagnosis of APS, but with positive serology.

The presence of bilateral optic retinopathy associated with progressive paraparesis and sensory abnormality of the limbs, first raised the possibility of CNS involvement. Retinal involvement has been found to range from 3 to 29% of SLE patients, depending on the population studied and the activity phase of the disease [13]. Although the exact pathogenesis is unclear, it is thought that immune complex deposition in the retinal and choroidal vessel wall are considered to be responsible for vasculitis [14]. In another situation, immune complexes may interact with platelet and/or endothelial cell surfaces, deposit in the vessel lumen and cause vascular occlusion in absence of inflammation (occlusive vasculitis). This may lead to profound ischemia, damaging retinal neurons and triggering neovascularization. It is different from the more common form, which is characterized by small arterial occlusions and diffuse capillary non-perfusion [15]. Although not a true vasculitis,

this severe form of retinopathy is believed to be associated with anti-phospholipid syndrome and has a poor visual prognosis. The latter seemed unlikely to be the cause of retinal damage in the present case, particularly considering the fact that ophthalmoscopy showed mild subclinical lupus microangiopathy changes, and also because our patient didn't have any abnormality characteristic of NPSLE on MRI or on neurologic exam. Moreover, there was complete resolution of macular edema on optical coherence tomography at 12 months follow-up.

Digital gangrene coexisting with SLE is uncommonly reported. Liu et al. found that 18 of 2,684 SLE patients had digital gangrene and Raynaud phenomenon, the long disease duration and elevated serum CRP may be predictive factors for SLE patients to develop the digital gangrene [16] There have been fewer reports of digital gangrene as initial manifestation of SLE. Rosato et al [17] had even asserted that digital ulcers and gangrene are never present as initial manifestation in SLE. However, Yang et al [18] had reported a case of acute gangrene of finger in an 8-year-old Korean girl without prior features of SLE. Cheah [19] had also reported a 33-year-old Chinese woman presenting with digital gangrene 3 weeks after the diagnosis of SLE. Other case reports have been documented from UK [20,21]. APS has been closely associated with lupus digital gangrene; the condition being seen in 3.3–7.5% of APS [22]. In our patient, active lupus disease with vasculitic manifestations together with positive antiphospholipid antibodies may play a role in the development of digital vascular lesions.

Therapeutic plasma exchange (TPE) in SLE patients was shown to be effective in reducing the anti-nuclear antibodies, anti-double-stranded DNA, restoration of normal complement level, and reducing the antiphospholipid antibodies [23]. While current EULAR guideline recommendations for the management of systemic lupus erythematosus support the use of TPE in patients with refractory cytopenias, thrombotic thrombocytopenic purpura (TTP), severe neurologic involvement and catastrophic APS [24], the American Society for Apheresis (ASFA) guideline consider TPE as a second-line therapy for SLE [25]. Typically, a course of 3-6 TPE sessions is enough to see response in patients with severe SLE complications.

We compared the therapeutic regimen and treatment responses for lupus vasculitis associated with positive aPL serology with different reports identified through systematic literature review. Thirty-four publications of case reports and case series from the English literature were reviewed. These publications dated from 1980 to 2022 and included 285 patients. Amongst the 34 included articles, there were 2 RCT [26,27]; however, these trials did not specifically focus on LV, but compared the efficiency of cyclophosphamide versus methylprednisolone in the treatment of severe neurologic manifestations in patients with SLE.

The highest number of patients came from a recent retrospective study that included patients with rheumatic diseases [28]. The most common indication for TPE was systemic lupus erythematosus, accounting for 50.2%. The TPE was performed in patients with SLE who suffered from lupus crisis, lupus nephritis, or in severe disease activity. Up to 62.9% SLE patients achieved partial remission and patients with complete remission accounted for 8.4%, which is an encouraging outcome, particularly in severe SLE or patients with involvement of kidney and or central nervous system.

Although retrospective case series and uncontrolled trial reported good response in patients with NPSLE receiving TPE, no RCTs has been done to investigate the efficacy of TPE in patients that had peripheral neuropathy secondary to SLE. A retrospective case series in 2003 reported 26 NPSLE patients that had received either TPE alone or TPE together with cyclophosphamide. Twenty patients (74%) improved after the treatment [29]. Another retrospective case series in 2007 reported a 100% response rate in NPSLE patients receiving TPE in combination with steroids and cyclophosphamide. Among the 10 patients with 13 episodes of NPSLE flares, 54% achieved complete remission and 46% achieved partial remission [30]. A prospective study published in 2000 followed 28 SLE patients while 18 of them suffered from NPSLE. However, concomitant use of other immunosuppressants making the evaluation of the efficacy of TPE alone difficult [27].

CONCLUSION

The nervous system involvement is one of the most complex and heterogeneous features of SLE. Disability from peripheral neuropathy is severe and requires prompt diagnosis and treatment to prevent progression. Occlusive vasculopathy is a rare but serious manifestation that can be seen at presentation in patients with aPL-positive SLE patients. The occurrence of vasculitis in our patient could have triggered the reaction of antiphospholipid antibodies with the negatively charged phospholipids flipped to the outer leaflet of endothelial cells by damage to these cells. The temporal association of our patients clinical improvement can be attributed to the initiation of plasmapheresis. Therefore, we suggest that early use of plasmapheresis may be of benefit and should be considered at an early stage in refractory cases of NPSLE.

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