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CASE REPORT

Acute pan-dysautonomia as well as central nervous system involvement and peripheral neuropathies in a patient with systemic lupus erythematosus

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Abstract A 32-year-old woman was diagnosed with leucopenia in 2002, being antinuclear antibody, anti-DNA antibody, and antiphospholipid antibody positive, and she was administered low-dose aspirin. In July 2006, she was admitted to our hospital because of pyrexia and abdominal pain. Examination revealed paralytic ileus, absence of the pupillary light reflex, dyshidrosis and anuresis. In addition, with high-level interleukin-6 in cerebrospinal fluid, the sensory nerve conduction velocity was derivation impotence. She was subsequently diagnosed with systemic lupus erythematosus (SLE) with central nervous system involvement, peripheral neuropathy as well as acute pan-dysautonomia. After pulse corticosteroid therapy, paralytic ileus was improved, however, the urination disorder persisted, and syncope due to orthostatic hypotension became marked. Plasma exchange and a second course of pulse corticosteroid therapy were performed, and were ineffective, whereas intravenous cyclophosphamide was effective. This patient is a rare case of central nervous system, peripheral neuropathy as well as acute pan-dysautonomia with SLE.

Keywords Acute pan-dysautonomia · Intravenous cyclophosphamide (IVCY) · Neuropsychiatric syndrome of SLE (NPSLE) · Systemic lupus erythematosus (SLE)

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystemic manifestations. Central nervous system (CNS) involvement has been reported to occur in 6–95% of SLE patients, depending on the criteria applied, [1, 2] however, the exact prevalence is probably between 6 and 12% [3].

Autonomic disorder is one of the 19 clinical syndromes in the American College of Rheumatology (ACR) classification of neuropsychiatric syndrome of systemic lupus erythematosus (NPSLE) [4]. The reported prevalence of autonomic neuropathy in SLE varies from no difference compared with controls [5] to a high prevalence [6–8] based on small case series and case-control studies. The majority of patients in these studies had mild subclinical dysautonomia in the presence of one or more abnormal cardiovascular reflex tests [7]. Reports on SLE with acute pan-dysautonomia are rare. In addition to neurological diseases, such as Shy–Drager and Guillain–Barré syndromes, autonomic neuropathy also includes symptomatic (secondary) autonomic neuropathy associated with diabetes, virus infections, hereditary diseases, and tumors (including paraneoplastic syndrome), as well as acute idiopathic autonomic neuropathy (AIAN) of unknown cause initially reported by Young et al. [9, 10]. As a result of constitutional, broad dysautonomia, various autonomic nerve signs, such as orthostatic hypotension, ileus, and dysuria, and a catatonic pupil usually occur in AIAN, the degree is advanced, [11] and motor, sensory, and CNS disorders are not present in principle [12].

We encountered a patient who acutely developed SLE with broad and advanced autonomic symptoms, exhibited various neuropathologies, such as CNS and peripheral

neuropathy, and responded well to intravenous cyclophosphamide (IVCY).

Case report

The patient was a 32-year-old woman with chief complaints of fever and abdominal pain, with no particular past or familial medical history. Regarding the history of the present illness, the patient visited the Dermatology Department of our hospital for cheek erythema in March 2002. Laboratory testing showed leucopenia (2,100 μl^{-1}), lymphopenia (560 μl^{-1}), hypocomplementemia, and positive antinuclear antibody (1:1,280), anti-DNA, and antiphospholipid antibody, and the patient was referred to our department. The patient met the SLE criteria, however, no active lesion was present and, thus, aspirin was administered at a low dose for the antiphospholipid antibody positivity, and the course was observed. On 21 July 2006, fever of 37.5°C and lower abdominal pain developed with no advance sign, and numbness and pain in both the hands and legs appeared the following day. The patient visited the hospital for aggravation of abdominal distension and pain. Ileus was diagnosed, and the patient was admitted emergently. On admission, she was in a markedly confused state. Body temperature was 37.8°C, but the heart rate was 60/min, showing relative bradycardia. Light and convergence reflexes were absent, and the tongue was dry. The abdomen was distended, tense and tympanitic. Sounds of intestinal peristalsis were absent over the abdomen. The skin was dry with anhidrosis. No deep tendon or abnormal reflexes were noted, and glove and stocking-type sensory abnormality was present. On laboratory testing on admission, white blood cells were 3,700 μl^{-1}; lymphocytes, 222 μl^{-1}; hemoglobin, 10.8 g/dl; platelets, 19.6 $\times$ 10^4 μl^{-1}; and erythrocyte sedimentation rate, 15 mm/1 h. Biochemical testing and urinalysis were normal. On immunoserological testing, CRP was 1.1 mg/dl; C3, 50 mg/dl (normal 86–160 mg/dl); C4, 4 mg/dl (17–45 mg/dl); and CH50, 13 U/ml (25–50 U/ml); indicating hypocomplementemia. Antinuclear antibody titer was 1:320 (homogenous, speckled); anti-cardiolipin antibody, 11 U/ml (normal value $<$ 8 U/ml); lupus anticoagulant (LAC) (dilute Russell's viper venom time), 1.83 ($<$1.3); and LAC (phospholipid neutralization), 10.7 s ($<$6.3 s); showing positivity. Anti-DNA antibody (RIA) was 2.9 IU/ml (normal value $<$ 6 IU/ml); anti-dsDNA antibody, 10 IU/ml ($<$10 IU/ml); anti-CLβ_2GPI, 2.2 U/ml ($<$3.5 U/ml); anti-RNP, (−); anti-Sm, (−); anti-SSA, (−); anti-SSB, (−); and antiribosomal P, (−); all normal values. Paralytic ileus was diagnosed on admission (Fig. 1). At the same time, disappearance of the light reflex, dyshidrosis, anuresis, respiratory sinus arrhythmia, and Valsalva test positivity were present, showing broad autonomic neuropathy. On admission, the patient was in acute confusional state, the cerebrospinal fluid (CSF) was clear with a normal opening pressure and contained 89 mononuclear cells/mm^3. Protein content of the CSF was 81 mg/dl (normal range 10–40 mg/dl) and the IgG index was 0.63 (normal range 0.20–0.85). The IL-6 level was markedly high (1,850 pg/ml). Oligoclonal bands were absent and all CSF cultures were negative. Electroencephalography showed diffuse slow waves. Brain and cervical/thoracic vertebral magnetic resonance imaging detected no abnormality. Sensory nerve conduction velocity was impossible to identify, with sural nerve, radial nerve, and ulnar nerve polyneuritis diagnosed, and NPSLE, mainly accompanied by autonomic neuropathy, however, also various neuropathologies, such as CNS and peripheral neuropathies, was diagnosed. Pulse corticosteroid therapy (intravenous infusion of

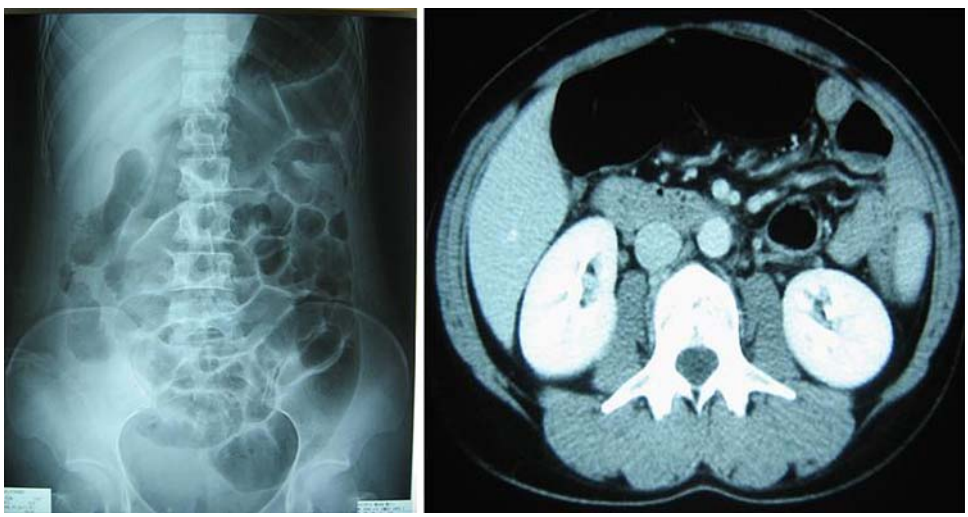

Fig. 1 Abdominal X-ray/CT on admission. The intestine and colon were markedly dilated, and paralytic ileus was diagnosed

methylprednisolone, 1,000 mg/day for 3 days) on the 3–5 days was performed, followed by prednisolone 60 mg/day, and the acute confusional state, paralytic ileus, and polyneuritis rapidly improved. The patient became capable of changing position, however, repeatedly lost consciousness in the standing position, revealing severe orthostatic hypotension. Voluntary micturition was hardly possible, and a large volume of urine was retained, making removal of the urethral catheter difficult. Hepatobiliary scintigraphy detected digestive tract dysfunction, which may have been a sign of autonomic neuropathy (Fig. 2a–c). Plasma exchange using 30 units of fresh frozen plasma on the 19, 27, 31, 34 days and a second course of pulse corticosteroid therapy on the 27–29 days were performed, however, were ineffective. CSF reexamination on the 41st day showed IL-6 1.6 pg/ml, TP 46 mg/dl, and improvement; however, hypocomplementemia persisted. IVCY (750 mg) was administered on the 55th day, thereafter, orthostatic hypotension and vesicorectal disorder resolved. Nausea persisted, even after the remission of paralytic ileus, and oral ingestion was difficult. The second course of IVCY on the 83rd day improved the symptoms on hepatobiliary scintigraphy (Fig. 2d–f), hypocomplementemia, which increased slowly, normalized, and all autonomic neuropathies improved. She was discharged with PSL 25 mg on the 101st hospital day (Fig. 3).

Discussion

This was a case of SLE that developed with broad autonomic signs. Autonomic neuropathy is included in the neuropathology of SLE, and its presence or absence has been investigated in some studies, [5–8] however, the number of reports is fewer than those on central nervous lesions and mental symptoms. ACR prescribes five objective tests to examine autonomic nervous function: postural change test, respiratory rate variation, Valsalva test positivity, and sweating test positivity [13]. This patient was positive for all items, and showed severe hypotension, inducing syncope in the standing position in the postural change test. The patient was admitted for paralytic ileus, however, at the same time, light and convergence reflexes were absent, and anuresis occurred several days later, indicating the acute onset of pan-dysautonomia, and the degree was severe. Two courses of pulse corticosteroid therapy resolved paralytic ileus, however, difficulty in oral ingestion due to nausea continued. Hepatobiliary scintigraphy identified reduced gallbladder contractility, which was improved by IVCY. For this patient, the effect of pulse corticosteroid therapy was insufficient, and IVCY was effective.

Complication of SLE by pan-dysautonomia is a rare pathology, and only four cases have been reported [14–17]. All reported cases showed acute onset, and the initial

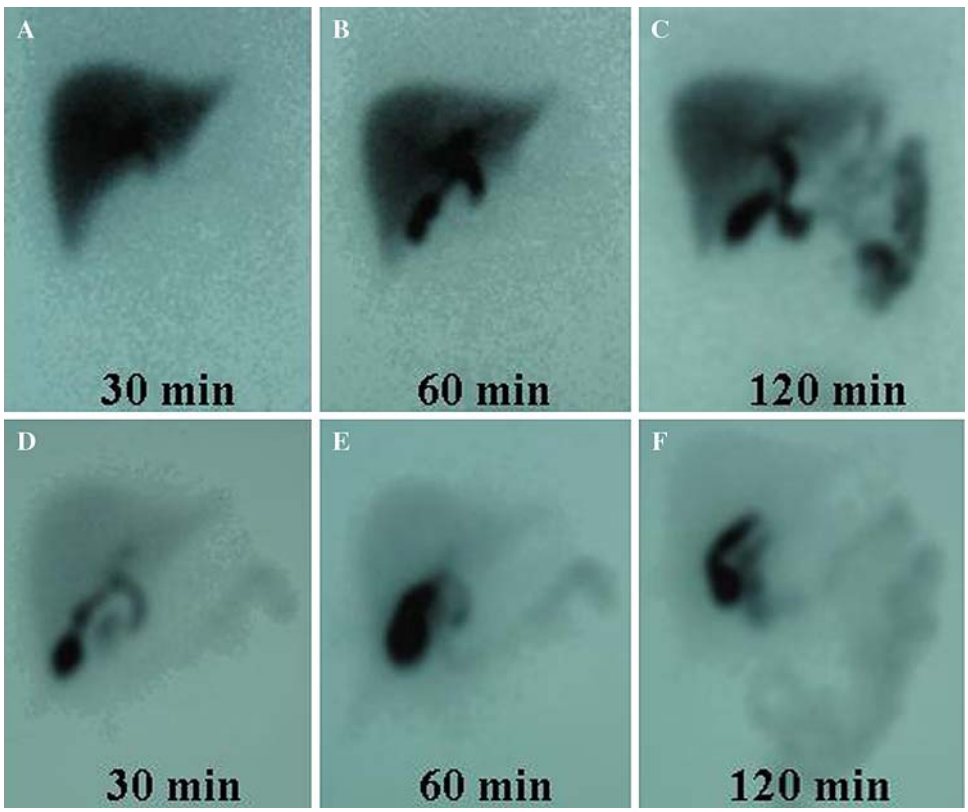

Fig. 2 **a–c** Hepatobiliary scintigraphy before IVCY. RI excretion from the liver parenchyma was markedly reduced. Gallbladder ejection fraction (GBEF) 30:4%, showing a marked reduction (normal: 40% or higher). **d–f** Hepatobiliary scintigraphy after IVCY. RI was excreted from the liver parenchyma. GBEF 30:40%, showing improvement

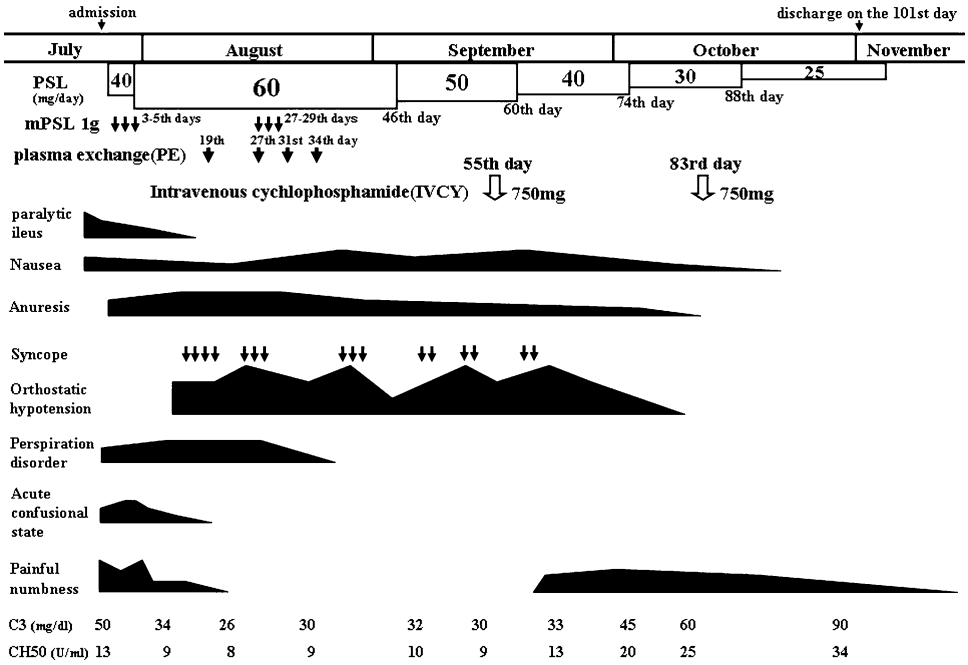

Fig. 3 Clinical course. *PSL* prednisolone, *mPSL* methylprednisolone, *IVCY* intravenous cychlophosphamide, *PE* plasma exchange

Table 1 Reported cases of systemic lupus erythematosus (SLE) with pan-dysautonomia

	This case	Law et al. [17]	Jodo et al. [16]	Arruda et al. [15]	Hoyle et al. [14]
Age/gender	32-year-old/F	28-year-old/F	42-year-old/F	72-year-old/F	21-year-old/F
Onset pattern	Acute	Acute	Acute	Acute	Acute
SLE development	Simultaneous	Simultaneous	Simultaneous	2-year earlier onset in CNS	Simultaneous
SLE lesion					
Skin eruption	NS	NS	NS	NS	NS
Arthritis	NS	Showed	Showed	NS	Showed
Serositis	NS	NS	NS	NS	NS
Proteinuria	NS	Showed	Showed	NS	NS
Central nervous system	Showed	NS	NS	NS	Showed
Peripheral nervous system					
Sensory	Showed	NS	NS	NS	NS
Motor	NS	NS	NS	NS	NS
Autonomic neuropathy					
Dyshidrosis	Showed	Showed	Showed	Showed	Showed
Impairment of light and convergence reflexes	Showed	NS	Showed	Showed	Showed
Orthostatic hypotension	Showed	Showed	Showed	NS	Showed
Dysuria	Showed	NS	Showed	Showed	Showed
Abnormal digestive tract function	Showed	Showed	Showed	Showed	Showed
Treatment	mPSL 1 g, PSL60 mg, PE (×4), IVCY (×2)	mPSL 0.5 g, PSL50 mg, AZA, HCQ	mPSL 1 g, PSL60 mg,	PSL80 mg, pyridostigmine	PSL, AZA
Curative effect	IVCY effective	Rapidly clinical response	Only constipation remained	Dryness, constipation remained	Rapidly clinical response

PSL prednisolone, *mPSL* methylprednisolone, *IVCY* intravenous, *AZA* azathioprine, *HCQ* hydroxychloroquine, *NS* not showed

symptom of SLE was autonomic neuropathy in three cases. In all four cases, the response of acute pan-dysautonomia to corticosteroid was very good. As well as acute pan-dysautonomia, only this patient showed CNS and peripheral neuropathy. This patient is exceptional as complicated acute pan-dysautonomia in SLE (Table 1). Our patient had been diagnosed with SLE based on skin eruption and immunological abnormality 3 years before the appearance of autonomic symptoms, and hypocomplementemia had persisted with no apparent organ disorder. On admission, severe autonomic neuropathy was noted, however, no characteristic clinical sign of SLE, such as skin eruption, arthritis, and nephritis was present, and anti-DNA antibody was also negative. However, acute confusional state, brainwave abnormality, and an increase in the CSF protein level were detected, based on which SLE was diagnosed. If the patient had not visited a medical institution, and the course before admission was not clear, the diagnosis of SLE would have been difficult.

Acute, broad, and severe autonomic neuropathy with no underlying disease is called AIAN [9–11]. AIAN and Guillain–Barré syndrome have many common points: acute onset, the presence of preceding infection in many cases, a high frequency of albuminocytologic dissociation, and the presence of serological inflammatory findings and inflammatory cell infiltration on nerve biopsy in some cases, [11, 18] and steroid treatment, plasma exchange, and massive γ-globulin administration have been applied from the viewpoint that immunological abnormality is present in the background. Recently, the presence of anti-ganglionic nicotinic acetylcholine receptor antibody in AIAN has been reported [19], and the disease concept, autoimmune autonomic neuropathy, has been proposed as a disease group that develops autonomic neuropathy via an autoimmune mechanism [20]. Guillain–Barré syndrome involves motor and sensory neuropathy accompanied by autonomic neuropathy, however, anti-ganglioside antibody is present, being recognized as an autoimmune disease targeting peripheral nerves [21]. The presence of patients with a high, specific antibody titer against mixed antigens of phospholipid and ganglioside or several gangliosides has been reported [22, 23]. Similarly, findings suggesting the involvement of autoantibodies, such as anti-NR2 glutamate receptor antibodies, in CNS lupus have been increasingly reported [24–27].

Unfortunately, we were not able to measure the titer of these autoantibodies; however, persistent hypocomplementemia suggested the involvement of autoantibodies in the onset of autonomic neuropathy. The neuropathies observed in this patient may also have resulted from autoantibodies.

Conflict of interest All of the authors confirm that there is no conflict of interest with regard to this work.

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