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Neuropsychiatric lupus with cerebral cortical lamellar necrosis: A case report

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease, and when it presents with neurological complications, it is termed neuropsychiatric systemic lupus erythematosus (NPSLE). Cortical laminar necrosis (CLN) refers to the necrosis of neurons in one or more layers of the cerebral cortex. This report presents a case of NPSLE with CLN in a 43-year-old female patient, diagnosis was based on clinical manifestations and MRI. The pathogenesis of CLN is complex, and its clinical presentations are varied. Thus, future research should focus on enhancing the understanding of this disease to improve its diagnosis and treatment.

Keywords: Systemic lupus erythematosus, neuropsychiatric lupus, lamellar necrosis of cerebral cortex, blood-brain barrier

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that involves many organs. SLE can involve the central, peripheral, or autonomic nervous system and have a wide range of neurological and psychiatric manifestations. When SLE involves neurological complications, it is termed neuropsychiatric systemic lupus erythematosus (NPSLE).[1] Research on NPSLE in humans is challenging due to the disease's high heterogeneity, making it the least understood manifestation of lupus, though it may be the most prevalent. The pathogenesis of NPSLE is multifactorial, involving inflammatory cytokines, autoantibodies, and immune complexes, resulting in vasculopathic, cytotoxic, and autoantibody-mediated neuronal injury.[2]

Cortical laminar necrosis (CLN) is defined as neurological necrosis, either focal or diffuse, in one or more cerebral cortices. This condition can involve the necrosis of neurons, glia, and blood vessels in the affected area.[3] Typical imaging findings include "lacing signs".[4] (Figure 1). Magnetic resonance imaging (MRI) serves two roles: first, as a diagnostic tool to visualize nervous system involvement and exclude other causes; second, as a prognostic tool to assess the lesions and monitor the disease's progression

CASE REPORT

A 43-year-old female patient was admitted to our hospital on July 25, 2022, due to weakness in her left lower limb. Her symptoms had persisted for more than 10 days and had worsened over the past 3 days. Physical examination revealed that the muscle strength of her left lower extremity was grade 4, and ataxia was observed. A craniocerebral computed tomography (CT) scan performed on July 17, 2022, prior to admission, revealed circular and quasicircular hypodensities of varying sizes in the parenchyma of the right frontal and temporal lobes, along with mass shadows of uneven density. (Figure 2). Following admission, cranial MRI with magnetic resonance angiography (MRA) and magnetic resonance spectroscopy (MRS) was conducted for further clarification (Figures 3-4). Extractable nuclear antigen (ENA) and antinuclear antibody (ANA) tests yielded the following results: anti-Smith (Sm) antibody, double-positive; antinuclear antibody, positive; anti-nucleosome, triple-positive; anti-double-stranded DNA antibody, double-positive; and anti-histone antibody, double-positive. ANA quantification showed nuclear homogeneity at 1:160 and nuclear granule type at 1:160. Additionally, immunoglobulin G was measured at 17.19 g/L (Table 1).

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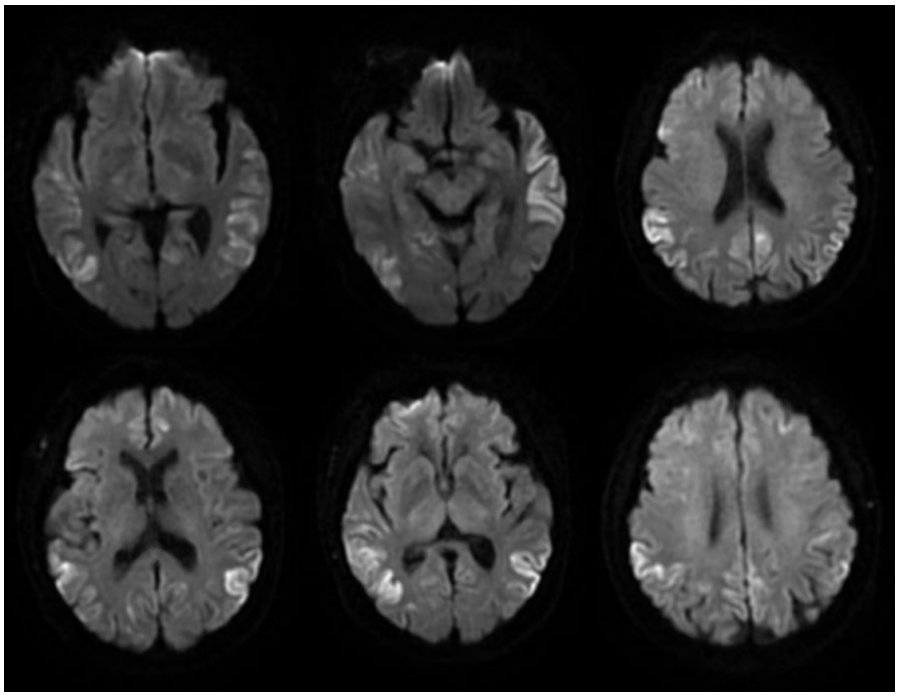

Figure 1. Diffusion-weighted magnetic resonance imaging (DWI) of the gyrus reveals spot-like hyperintensity in multiple cortical areas of both cerebral hemispheres.

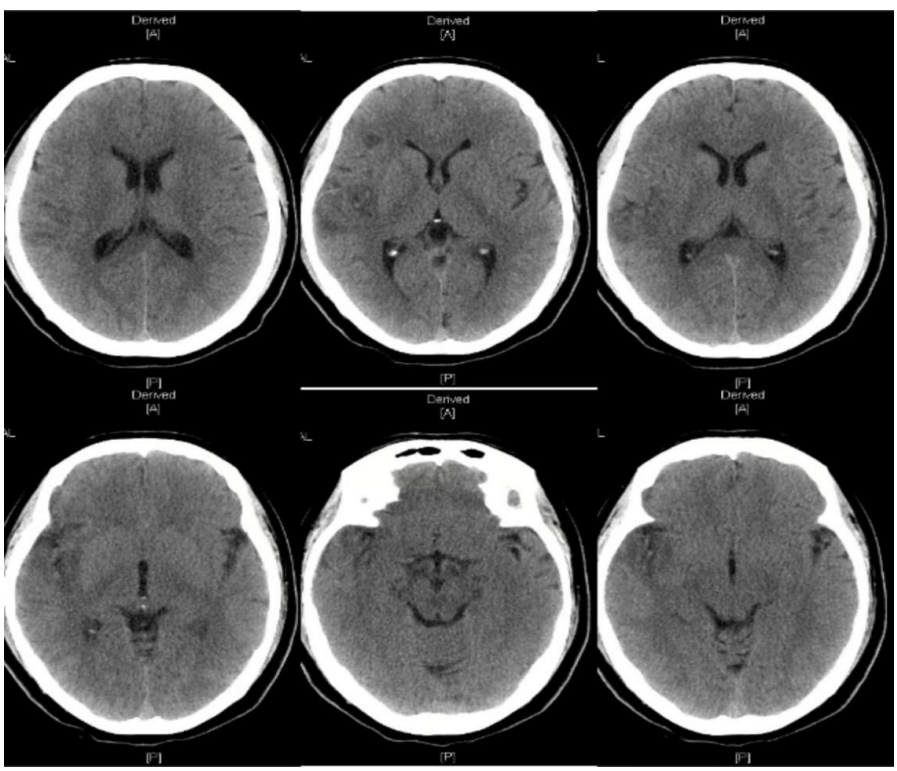

Figure 2: Brain computed tomography (CT) performed on July 17, 2022, revealed circular and quasicircular hypodensities of varying sizes in the parenchyma of the right frontal and temporal lobes, along with mass shadows of uneven density.

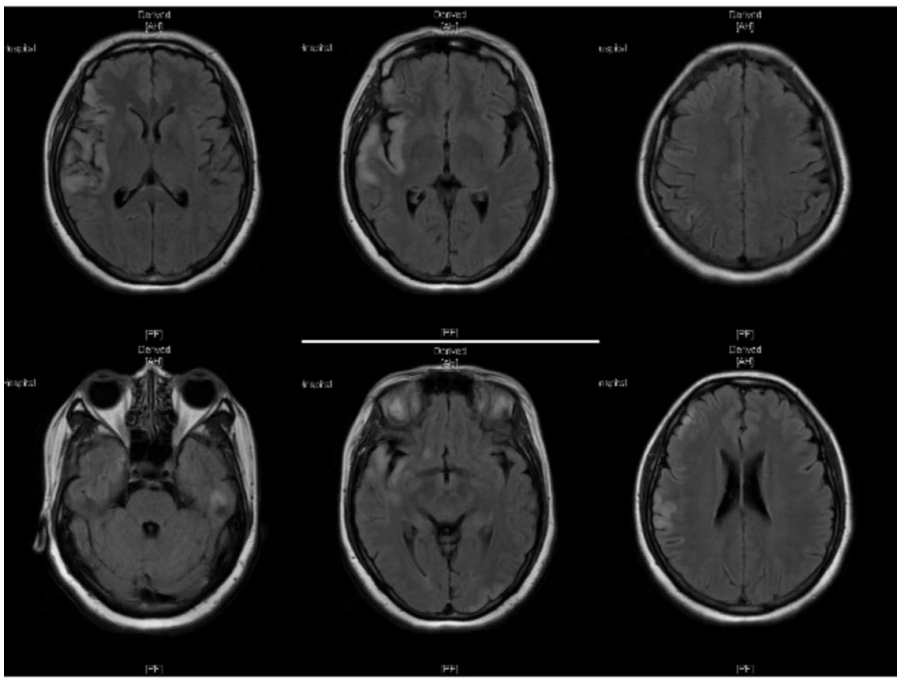

Figure 3. MRI performed on July 25, 2022, showed elevated T2 fluid-attenuated inversion recovery (FLAIR) signals in the bilateral frontotemporal lobes, right parietal lobe, insular lobe, and left occipital lobe. Additionally, local gyrus thickening and swelling were observed in the right frontotemporal lobe.

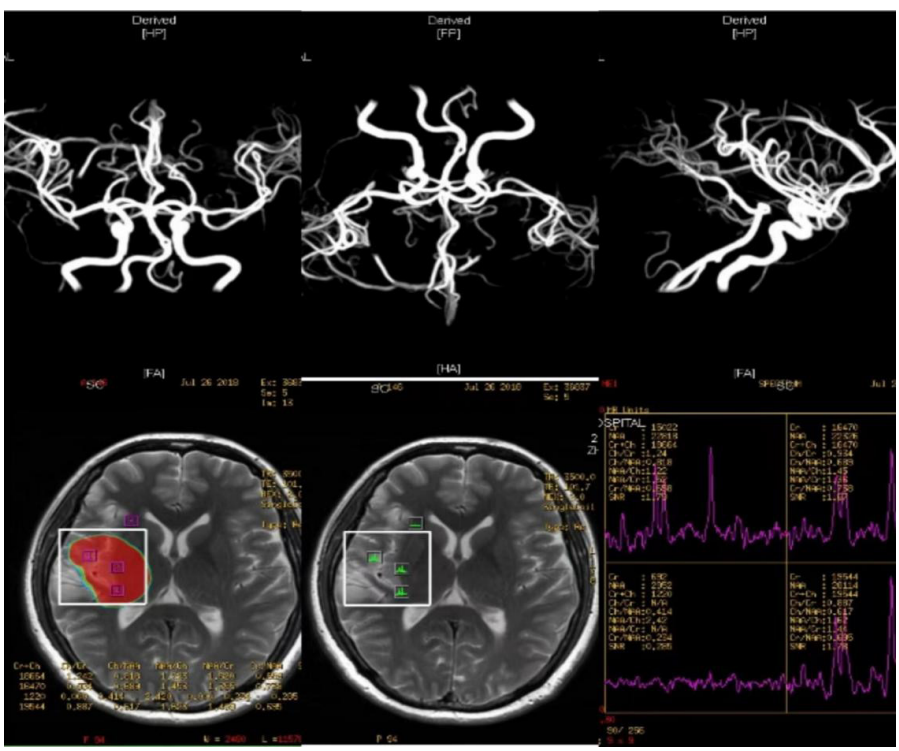

Figure 4. On July 25, 2022, no obvious abnormalities were observed on craniocerebral magnetic resonance angiography (MRA). Magnetic resonance spectroscopy (MRS) revealed abnormal signal foci in the right insula, with a slight decrease in Cr and a Cho/Cr ratio of 1.24.

Table 1: Extractable nuclear antigen (ENA), antinuclear antibody (ANA), and other immunological indicators

Report Project	Result	Reference Values
Antinuclear antibody	positive	negative
Anti-U1- snRNP antibody	negative	negative
Anti-SSA/Ro52 antibody	negative	negative
Anti-SSA/Ro60 antibody	negative	negative
Anti-SSB/La antibody	negative	negative
Anti-Ku antibody	negative	negative
Anti-Mi-2 antibody	negative	negative
Anti-Sm antibody	double-positive	negative
Anti-Scl-70 antibody	negative	negative
Anti-PM-Scl antibody	negative	negative
Anti-Jo-1 antibody	negative	negative
Anti-kinetochore B antibody	negative	negative
Anti-proliferative cell nuclear antigen antibody	negative	negative
Anti-nucleosome antibody	triple-positive	negative
Anti-histone antibody	double-positive	negative
Anti-ribosomal P protein antibody	negative	negative
Anti-mitochondrial M2 antibody	negative	negative
Anti-double stranded DNA antibody	double-positive	negative
Immunoglobulin G	17.19 g/L	7–16 g/L
Antinuclear antibody (ANA) quantified	nuclear homogeneity (1:160) + nuclear particles (1:160)	<1:100

The patient was diagnosed with NPSLE based on clinical manifestations and test results. She was treated with high dose prednisolone sodium succinate (500 mg) and immunoglobulin. Additionally, she received hydroxychloroquine and cyclophosphamide for immune regulation. The patient was advised to abstain from alcohol and was prescribed calcium carbonate D3 pills to prevent hormone-induced osteoporosis. Omeprazole was administered to protect the gastrointestinal mucosa, along with other symptomatic and supportive treatments. After discharge, her treatment continued with oral hydroxychloroquine and methylprednisolone, along with other medications as directed by her doctor. Follow-up brain MRIs were performed on September 16, 2022 (Figure 5), April 17, 2023 (Figure 6), and April 23, 2024 (Figure 7), revealing significant abnormal findings on fluid-attenuated inversion recovery (FLAIR) sequences.

DISCUSSION

Two main mechanisms of CLN have been proposed: vascular distribution and heterosensory selection. The vascular distribution mechanism suggests that cortical vessels are particularly susceptible to ischemia and hypoxic lesions. The pathological lamellar distribution of these lesions aligns with the cerebral cortical capillary distribution, where abnormal morphology or dysfunction of the capillaries affects the blood and oxygen supply to neural tissues.[5] The heterosensory selection mechanism suggests that neurotransmitters and receptors located in different areas of the gray matter or different types of neurons can have varied chemical structures. Disruption in these areas may cause ischemia-hypoxia, oxidative stress, excitatory amino acid toxicity, blood-brain barrier damage, nerve inflammation, and interactions among various other factors. Furthermore, the tolerance of gray matter is lower than that of white matter, particularly in the first three layers of the gray matter, which are the most vulnerable. In the cerebral cortex, this damage is more pronounced on the sides and the bottom of the sulci than on the surface of the gyrus.[6]

The main mechanism of CLN induced by NPSLE

Microvascular disease

Immune complex deposition and complement

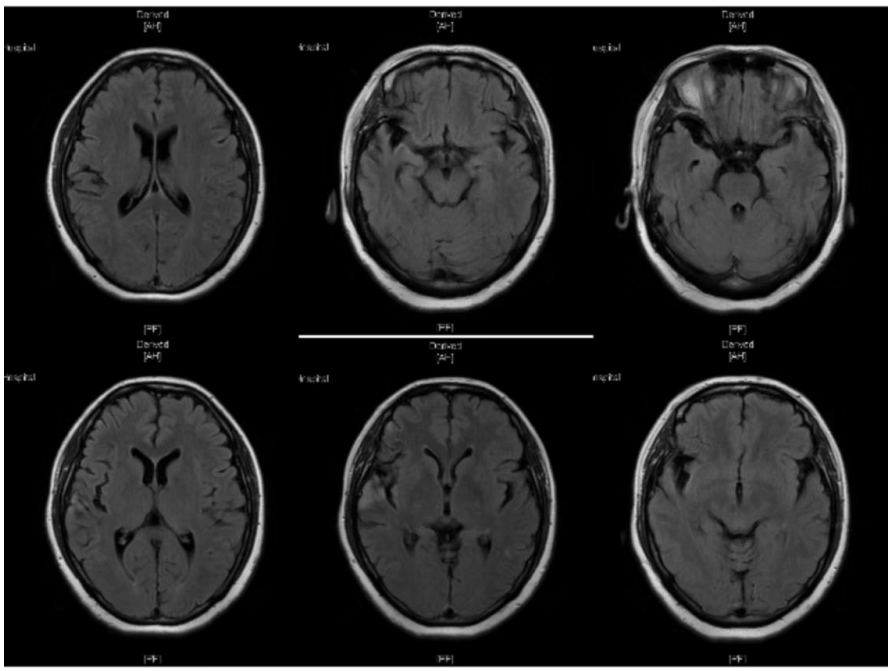

Figure 5. Compared to the MRI on August 4, 2022, the MRI on September 16, 2022, revealed multiple plaques in the right frontotemporal lobe and left occipital lobe, with flaky abnormal signals in the gyrus, slight FLAIR hyperintensity, and a reduction in the anterior range.

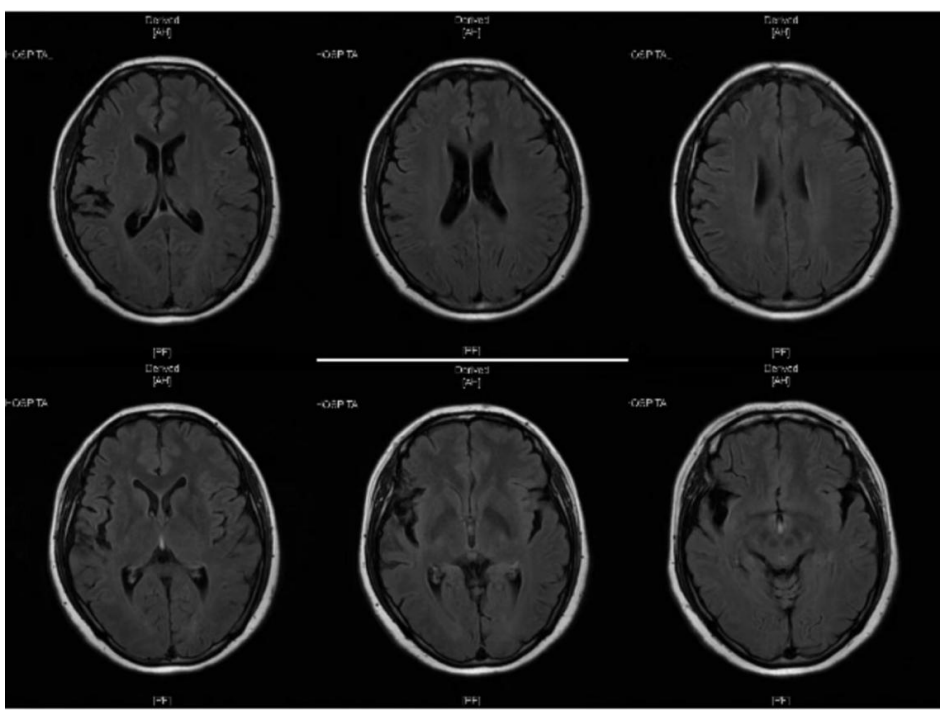

Figure 6. MRI performed on April 17, 2023, showed multiple flaked spots and gyrus FLAIR with slightly elevated signals in the right frontotemporal parietal lobe and the left fronto-occipital subcortical area. The range of these abnormalities was reduced compared to the findings on September 16, 2022.

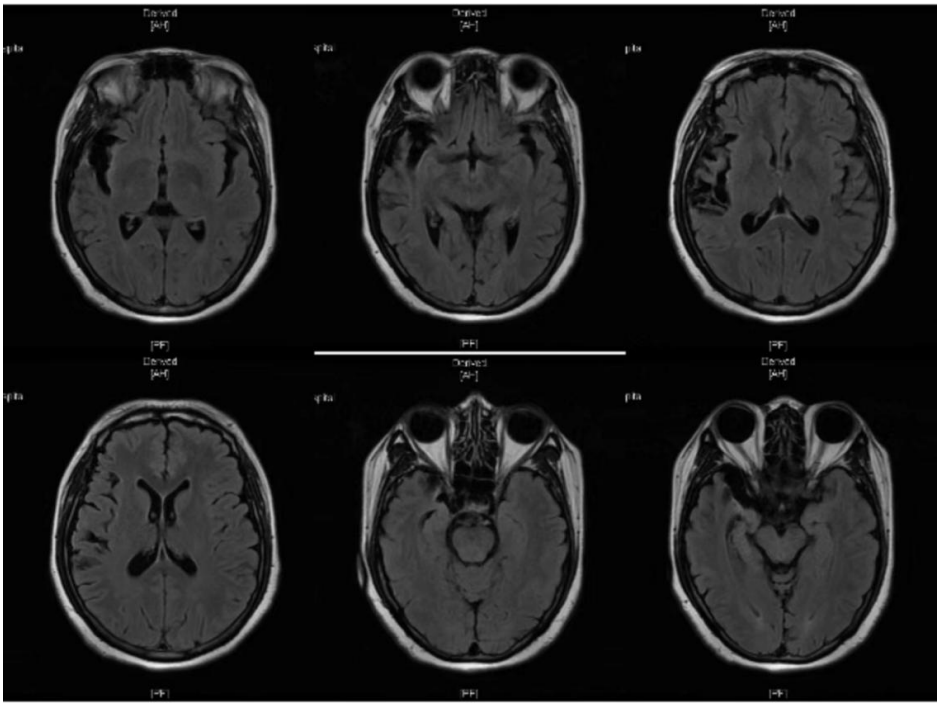

Figure 7. MRI performed on April 23, 2024, showed bilateral, sporadic patchy FLAIR with slight hyperintensity in the frontal lobe.

activation are responsible for microangiopathy in patients with NPSLE. These processes lead to the dissolution and necrosis of microvascular endothelial cells, the destruction of the blood-cerebrospinal fluid barrier, increased permeability, and the release of many autoantigenic substances into the blood, promoting autoantibody production. Extensive microvascular disease can result in various pathologies, including microvascular embolism, cerebral infarction, hemorrhage, cortical atrophy, ischemic demyelination, and multiple sclerosis.[7] If microvascular embolization occurs, it can cause abnormal perfusion, decreased material exchange capacity, tissue hypoxic edema, insufficient neurotrophic supply, and increased neuronal load.[8]

Histologically, the cerebral cortex is generally divided into six layers: the molecular layer, the outer granular layer, the pyramidal cell layer, the inner granular layer, the ganglion cell layer, and the polymorphic layer, listed from outermost to innermost.[9] Neuron types in the cerebral cortex are classified as either pyramidal or nonpyramidal cells. The blood flow in the gray matter of brain tissue is typically higher than in the white matter, with the cerebral cortex receiving the highest blood supply, followed by the basal nuclei and the cerebellar cortex. Additionally, different cell types exhibit varying sensitivities to ischemia and hypoxia, with neurons being the most sensitive, followed by astrocytes, oligodendrocytes, and endothelial cells. Among neurons, those in cerebral cortex layers III, V, and VI; hippocampal pyramidal cells; and cerebellar Purkinje cells are the most sensitive. Therefore, when NPSLE involves microangiopathy, the cerebral cortex is prone to laminar necrosis.

Blood–brain barrier (BBB) disruption

Disruption of the blood-brain barrier (BBB) is one of the main pathogeneses of NPSLE.[10] The BBB is primarily composed of brain capillary endothelial cells, basement membranes, and astrocyte foot processes. It maintains the normal activity and function of the central nervous system and protects neurons from potential neurotoxic substances in the circulation.[11] Damage to the BBB is a key component of the neuropathological changes in SLE. Tumor necrosis factor (TNF)-related weak inducer of apoptosis (TWEAK), complement C5a, anti-NMDA receptor antibody, and anti-glucose-regulated protein (GRP) 78 antibody in the serum can act on the BBB in patients with SLE and activate downstream signaling pathways, leading to increased permeability and allowing neurotoxic substances to enter the cerebrospinal

fluid, further damaging neurons.[12,13]

Structural and functional damage to the BBB can cause vasogenic brain edema and increase local intracranial pressure, leading to decreased cerebral blood flow, brain cell necrosis, and brain tissue ischemia and hypoxia, further aggravating BBB damage. Tight junction-associated proteins, the main structural proteins of tight junctions, play an important role in maintaining BBB function.[14] Mild BBB disruption is associated with the disruption of cellular pathways, whereas severe BBB disruption is mediated by the disruption of tight junction cells, leading to intracellular edema in the cortex, where energy consumption and lack of blood supply facilitate the development of CLN.

Neuroinflammatory reaction

SLE causes the immune system to attack the tissues and organs, inducing the release of type 1 interferon-alpha from leukocytes, which triggers a series of immune processes by binding to receptors in different tissues.[15] A previous study found that sufficient type 1 interferon α can cross the BBB and cause the microglia to attack the synapses in the brain, leading to synapse loss in the frontal cortex.[16] Damaged neurons release chemokines, increasing the number of central immune cells and promoting pro-inflammatory cytokine secretion. The differentiation of microglia to the M1 phenotype also produces inflammatory cytokines, increasing the expression of downstream signaling molecules. This promotes inflammation, increases protein levels in the acute phase, induces BBB damage, aggravates cerebral edema, and leads to apoptosis.[17] The healthy BBB can protect the cerebral cortex from the peripheral immune response, but after BBB destruction, blood-derived inflammatory factors can enter the brain and stimulate the glial cells, subsequently causing a neuroinflammatory reaction leading to CLN.

In conclusion, we report here a case of NPSLE presenting with CLN which was not explicitly reported before so far. The patient's condition significantly improved with early detection and treatment. The pathogenesis of CLN is complex, and its manifestations are diverse. Therefore, future studies should aim to enhance the understanding of this disease to improve diagnosis and treatment.

DISCLOSURE

Conflict of interest: None

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