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LETTER TO THE EDITOR Open Access

A Chinese child with both systemic lupus erythematosus coexisting with neuromyelitis optica spectrum disorder: a case report

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Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease or and one of the most heterogeneous illnesses characterized by differences in autoantibody profiles, serum cytokine levels, and multisystem involvement; SLE is commonly characterized by clinical manifestations of the skin and the musculoskeletal, renal, hematological, and neuropsychiatric (NP) systems [1–3]. NP symptoms occur in 37 to 95% of patients during the course of SLE [4].

Neuromyelitis optica spectrum disorders (NMOSD) are antibody-mediated inflammatory autoimmune disorders of the central nervous system (CNS) [5–7]. NMOSD are characterized by recurrent inflammatory events that involve primarily the optic nerves and the spinal cord but also affect other regions of the CNS, including the hypothalamus, area postrema and periaqueductal gray matter [8]. The involvement of these areas in the CNS can lead to optic neuritis (ON), acute myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome and symptomatic cerebral syndrome [9]. In ≥80% of cases, NMOSD is caused by pathogenetic IgG autoantibodies that target aquaporin 4 (AQP4-IgG), which is the most abundant water channel protein that is expressed on the end-feet membranes of astrocytes along the blood–brain barrier (BBB) and in Müller cells that are distributed on the fovea centralis in the retina [9–11]. The presence of AQP4-IgG is highly specific and differentiates NMOSD from multiple sclerosis [12, 13].

Although the coexistence of SLE and NMOSD in adults is well recognized by both rheumatologists and neurologists [14], SLE coexisting with NMOSD in children is very rare. Therefore, further investigation of the relationship between SLE and NMOSD is needed to elucidate all the clinical aspects of their coexistence in children. We describe an additional case of a child with SLE coexisting with NMOSD and compare this case to previous reports via a literature review to better understand this condition.

The patient, a 14-year-old Chinese girl, presented with fever in July 2022. She was referred to our hospital for evaluation because of persistent thrombocytopenia and proteinuria in August 2022. Physical examination revealed anemic appearance and edema. Other physical findings were unremarkable. Her medical history and family history were also unremarkable. Laboratory tests revealed anemia (hemoglobin 76 g/l, normal range 110–160 g/l), increased reticulocyte count (140×10^9/l, normal range 24–84×10^9/l), thrombocytopenia (57.0×10^9/l, normal range 100–300×10^9/l), 2+proteinuria, elevated

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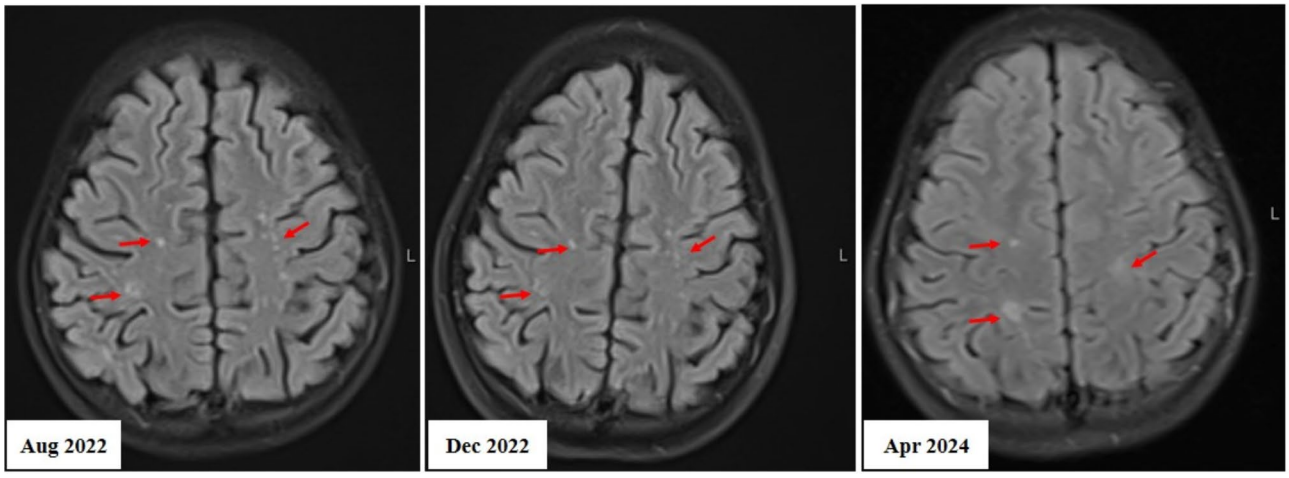

Fig. 1 Brain of MRI. Red arrow: demyelinating lesions

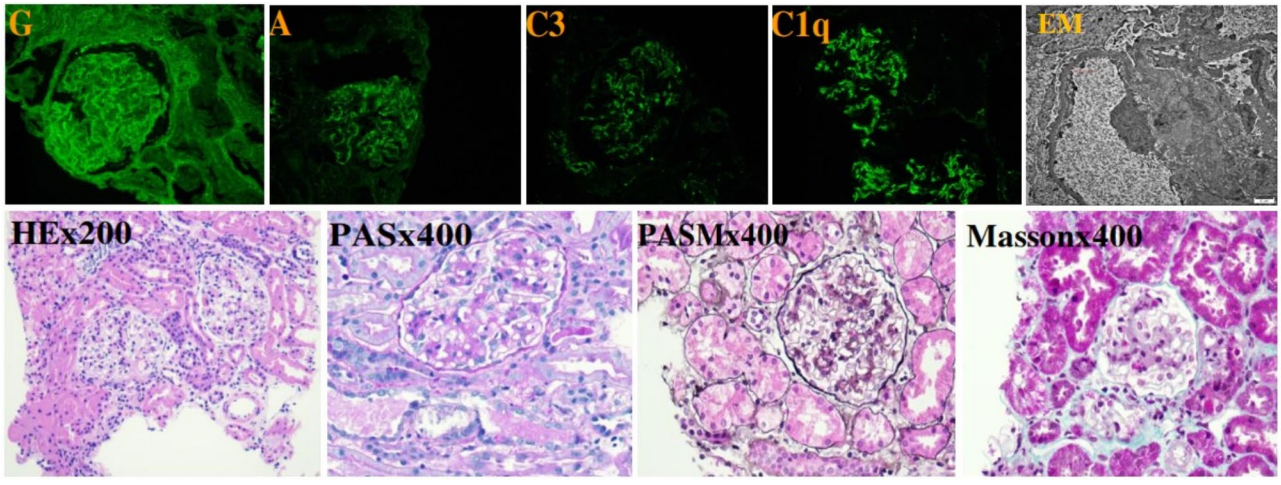

Fig. 2 Renal biopsy showed lupus nephritis type III under light (×400, HE×200), electron (×11600) and Immunofluorescence (×400) microscopy in patient. G: immunoglobulin G, A: immunoglobulin A

lactic dehydrogenase (LDH) levels (541 U/L, normal range 80–285 U/L), and decreased serum albumin levels (23.1 g/L, normal range 39–45 g/L). The levels of complement 3 and 4 were both low. The 24-h urine protein concentration was 0.56 g (normal < 0.15 g/24 h), and the random urine protein/creatinine (UPr/Cr) ratio was 1.2 mg/mg. Autoantibody test results revealed positive results for ANA (1:640), SSA, SSB, and the direct Coombs test. Lupus anticoagulant (LAC), anti-β2 glycoprotein-I antibody (anti-β2GPI), anticardiolipin antibody (aCL), immunoglobulin G (IgG) immunoglobulin M (IgM), and other test results were negative. MRI of the brain revealed scattered demyelinating lesions in the frontal and parietal lobes (Fig. 1. A). The electroencephalogram results were abnormal, but there were no sharp or slow waves. Lung CT revealed pleural effusion, and the lung function test was normal. Kidney biopsy was performed because of persistent proteinuria, and the findings revealed positive immunofluorescence (IF) staining for immunoglobulin A (IgA,+), IgM (2+), IgG (2+), C3(+~2+), and C1q (3+) and negative IF staining for fibrinogen (Fib), ALB, and C4c (Fig. 2); additionally, a moderately increased mesangial matrix and mesangial hypercellularity were detected via light microscopy, and electron dense substance deposition was observed in the glomerular mesangial area and segmental capillary loop basement membrane endothelium via electron microscopy (Fig. 2). The renal biopsy findings met the International Society of Nephrology/Renal Pathology Society classification (ISN/RPS) class III lupus nephritis (LN).

The patient was diagnosed with SLE and LN. She was treated with intravenous methylprednisolone (48 mg/day) followed by oral prednisolone (60 mg/day) and hydroxychloroquine (5 mg/kg/day) combined with monthly intravenous cyclophosphamide (CTX) pulses (500 mg/m^2) and intravenous belimumab (10 mg/kg,

every 2 weeks three times and then every 4 weeks) as induction therapy. Other treatments included oral enalapril and aspirin. The platelet count returned to normal as soon as possible, the levels of complement C3 and C4 were restored to normal one month later, proteinuria disappeared, and the 24-hour urine protein level was normal two months later. After 6 pulses of CTX, the patient started maintenance therapy with oral mycophenolate mofetil (MMF, 0.5 g every 12 h) and continued intravenous belimumab (10 mg/kg every 4 weeks) and oral prednisolone (5 mg/d). She achieved complete remission at 2 months of follow-up and was in stable condition, with complete remission during maintenance therapy. During follow-up, MRI of her brain still revealed demyelinating lesions in the frontal and parietal lobes, which had not worsened (Fig. 1 B).

The patient suffered sudden vision loss in May 2024. Neuroophthalmology examination revealed visual acuity of 20/30 in the left eye (OD) and 20/40 in the right eye (OS), with a right relative afferent pupillary defect (RAPD). The color vision (Hardy–Rand–Rittler) was 5/14 OD and 4/14 OS. Intraocular pressures were within normal ranges in both eyes. Slit-lamp examination was unremarkable. Extraocular motility was full, but the patient experienced left-eye discomfort with eye movements. Optical coherence tomography revealed that the bilateral optic disc had light color, unclear boundaries and edema (Fig. 3), which were observed in optic neuritis (ON). Orbital MRI was normal, but MRI of the brain revealed that the scattered demyelinating lesions in the frontal and parietal lobes were exacerbated (Fig. 1C). Cerebrospinal fluid analysis was normal. The patient was positive for anti-aquaporin-4 (AQP4) antibodies (cell-based assay, CBA), with a titer of 1:100, and was negative for anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in her serum. She was diagnosed with NMOSD on the basis of a positive test for AQP-IgG and optic neuritis and was treated with intravenous pulse methylprednisolone (IVMP) at 500 mg per day for 3 consecutive days. After two courses of IVMP, therapeutic plasma exchange (TPE) was performed because of a poor response to IVMP, once on alternate days three times. Her vision improved with TPE. She continued to receive IVMP at 250 mg per day for 3 consecutive days combined with intravenous immunoglobulins (IVIGs) at 400 mg/kg per day for 5 consecutive days. Her vision gradually returned to normal after acute treatment. The lesions of the bilateral optic disc improved significantly through optical coherence tomography (Fig. 3). Tocilizumab was administered for preventive treatment after acute treatment.

In the present study, we describe a 14-year-old child who suffered from SLE coexisting with NMOSD. The patient met the 2019 European League Against Rheumatism/American College (EULAR/ACR) of Rheumatology Classification Criteria for SLE [15] on the basis of positive ANA (1:640); autoimmune hemolytic anemia (four points), thrombocytopenia; proteinuria, ISN/RPS class III LN (10 points); pleural effusion (five points); and low levels of C3 and C4 (four points). The patient's total score was 23 points, which is more than 10 points. She was diagnosed with SLE and LN. Although MRI of the brain revealed scattered demyelinating lesions in the frontal and parietal lobes, we did not make a diagnosis of neuropsychiatric SLE (NPSLE) because of the lack of symptoms suggesting neurological involvement. The patient achieved complete remission during induction therapy. The scattered demyelinating lesions in the frontal and parietal lobes did not disappear, and they were not exacerbated, as shown by MRI of the brain during follow-up (Fig. 1 B).

During complete remission of SLE, the patient suffered sudden vision loss in May 2024 and was shown to be positive for anti-AQP4 antibodies and negative for anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in the serum. MRI of the brain revealed that the scattered demyelinating lesions in the frontal and parietal lobes were exacerbated compared with previous findings. Therefore, she met the modified IPND 2015

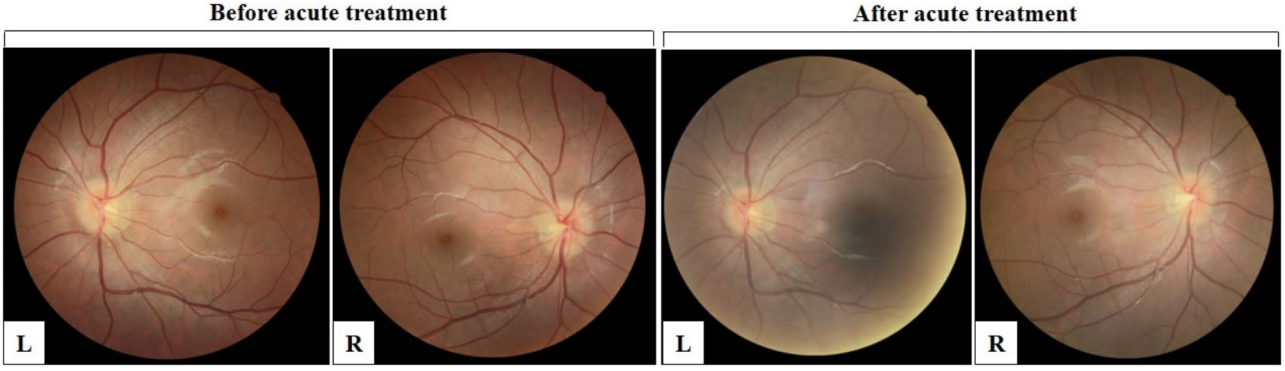

Fig. 3 Optical Coherence Tomography. The bilateral optic disc display light color, unclear boundaries and edema before acute treatment. They improved significantly after acute treatment

NMOSD criteria [16] on the basis of a positive test for AQP-IgG via an available detection method (cell-based assay, CBA), ON and nonspecific demyelinating lesions as revealed by brain MRI. The patient was diagnosed with SLE coexisting with NMOSD. After the diagnosis of NMOSD, acute treatment was administered. Her vision gradually returned to normal after acute treatment.

SLE is a systemic autoimmune disease that can affect any organ of the body, while NMOSD is an autoimmune inflammatory disorder of the CNS that affects the spinal cord, optic nerves, and certain brain regions [17, 18] and can be considered a single-organ autoimmune disease. Most current evidence suggests that NMOSD is best described as a CNS astrocytopathy [19–21].

Although corticosteroids, CTX, azathioprine, MMF, rituximab, TPE, and IVIG are used to treat both SLE and NMOSD, the treatment strategies for these two diseases differ. Most patients with NMOSD develop relapsing attacks of CNS inflammation, which can lead to serious disability and mortality and require indefinite immunosuppression [22, 23]. Several new therapies (inebilizumab, eculizumab, and satralizumab) have recently been approved specifically for preventing the recurrence of NMOSD, and these treatments significantly improve the prognosis of patients with this disease [24]. Therefore, timely diagnosis of NMOSD is critical, as patients may benefit from acute treatment tailored specifically to NMOSD as opposed to SLE.

Distinguishing NMOSD from SLE with CNS involvement is very important for the early diagnosis and treatment of NMOSD. Neurological manifestations, particularly optico-spinal involvement in SLE, can be caused by coexisting NMOSD. Patients with this condition can present with any of the six core manifestations of NMOSD, which can mimic the central NP manifestations of SLE. Optic neuritis (37–54%) and myelitis (30–47%) are common manifestations in NMOSD patients [25, 26]. However, they are less common in patients with SLE (1–2.1%) [27, 28]. Moreover, the two diseases have different autoantibody profiles. Antibodies against the subunits of the N-methyl-D-aspartate (NMDA) receptor (anti-DNA/NR2) and anti-ribosomal P antibodies (anti-ribosomal P) are considered to target specific parenchymal structures in the brain and underlie the onset of NPSLE [29]. Anti-Sm antibodies (anti-Sm), anti-U1-ribonucleoprotein antibodies (anti-RNP) and anti-ribosomal P increase the production of inflammatory cytokines in SLE [29]. In addition, autoantibodies that are potentially relevant to NPSLE include anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH), anti-supra-basin (SBSN), anti-brain cytoplasmic ribonucleic acid (BC RNA), and anti-ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1), which can be helpful markers for diagnosing NPSLE or distinguishing NPSLE from SLE in the absence of NP symptoms [30]. Anti-AQP4 antibodies are a diagnostic marker for NMOSD with high specificity, occur in 70–90% of patients with NMOSD and contribute to distinguishing NMOSD from NPSLE [9, 31].

Although our patient had demyelinating lesions that were detected by brain MRI, there were no NP symptoms, which is why the patient was not tested for AQP4-IgG and MOG-IgG. The authors agreed that SLE patients with demyelinating lesions as revealed by brain MRI or NP symptoms should be tested for AQP4-IgG and MOG-IgG to help identify comorbid SLE and NMOSD.

NMOSD is rare in children and adolescents, and approximately 3–5% of NMOSD cases are reported to have pediatric onset before 18 years of age [32]. The most common presenting features of NMOSD are visual, motor, sensory and constitutional symptoms (such as vomiting, fever, and seizures). In most reports of pediatric NMOSD, ON was the first clinical event in 43-47% of patients, and TM occurred in 24-36% of patients, either alone or in combination [33]. Other symptoms include ataxia, encephalopathy, and cranial nerve dysfunction, such as ophthalmoparesis or area postrema syndrome. The coexistence of NMOSD with certain systemic diseases, such as autoimmune hypothyroidism, myasthenia gravis, SLE or Sjogren's syndrome (SjS), is now well established [34]. Among these systemic diseases, NMOSD is more likely to coexist with SLE, with a probability of 1/5,000,000 [35]. Similar cases have been reported in greater numbers in adults, but cases in children are still rare. Our data revealed NMOSD in <1% of all children with SLE (unpublished). To date, 10 children with SLE coexisting with NMOSD have been reported in PubMed (Table 1) [36–39]. Three were case reports that included our patient, and two cohort studies included seven patients [35–38], which suggests that NMOSD is very rare in children with SLE. Girls are more often affected, with a male to female ratio of 9:1 [36–39]. Among these 10 patients, two patients experienced NMOSD after the onset of SLE with a median of 3 years between the two diagnoses, two patients first manifested as NMOSD followed by SLE with a median of 7.5 years between the two diagnoses, and the others had SLE and NMOSD at the same time [36–39].

In this study, clinical data concerning SLE were unavailable for one patient and were available in detail for nine patients; seven of nine (77.8%) patients had hematologic involvement, and two (P1 and P5) had kidney involvement manifesting as nephritis. Hematological manifestations were also observed in the majority of adult patients (63%) [40].

Among the core manifestations of NMOSD, most (7/10) involve the eyes and present as ON or retinal vasculitis [36–39]. Interestingly, although neurological symptoms were observed in two patients (P2 and P10),

Table 1 Clinical feature of SLE coexisting with NMOSD in children

P	A1	G	Clinical features of SLE	Positive anti-bodies	Therapy for SLE		A2	Clinical features of NMOSD				Therapy for NMOSD		
					Induction therapy	Mainte-nance therapy		Phenotype	Spine MRI	Brain MRI	Positive anti-AQP4	Acute therapy	Preventive therapy	Out-come
1	14	F	Fever, Hemolytic anemia Thrombocytopenia Proteinuria (LN) Pleuritis Hypocomplementemia (C3 and C4)	ANA Anti-SSA Anti-SSB Coombs test	Prednisone CTX HCQ	Prednisone MMF HCQ	16	ON	Swelling of the spinal cord at the levels of c2-6	Scattered demyelinat-ing lesions in frontal and parietal lobes	Y(1:100) in serum	IVMP TPE IVIG	Tocilizumab Prednisone	CR
2 [35]	5	F	Fever Pancytopenia Recurrent parotiditis liver dysfunction (jaundice, elevated ALT and AST) Hypocomplementemia (C3 and C4)	ANA Anti-SSA Anti-SSB Anti-cardio-lipin RF	Prednisone MMF	MMF Tacrolimus Rituximab HCQ	9	ON	Swelling of the spinal cord at the levels of c2-6	Obvious small of the left optic nerve	Y(1:3200) in serum Y(1:100) in CSF	IVPMP	Prednisone Rituximab MMF Tacrolimus	PR
3 [36]	12	M	Arthritis Pancytopenia with haematological picture of secondary MAS Lung vasculitis on biopsy, Retinal vasculitis Psychotic episode with hallucinations	ANA Anti-dsDNA Anti-C1q	IVMP CTX Rituximab Etoposide	MMF HCQ	12	Retinal vasculitis	Normal	Long stand-ing infarcts of right caudate nucleus and dorsal right lentiform nucleus Generalized progressive atrophy	Y in serum	IVMP CTX Rituximab	MMF	CR
4 [36]	11	F	Malar rash Raynaud phenomenon Myositis Lung involvement Haematological disease (leukopenia, neutropenia) Family history of SLE (father, paternal aunt)	ANA Anti-RNP Anti-Ro	CS Rituximab	AZA MTX	11	Persistent headaches	LETM	Non-specific lesion subcortical frontal and parietal white matter	Y	CS Rituximab	AZA MTX	PR
5 [36]	9	F	Non-specific gastro-intestinal Symptoms Tubulo-interstitial nephritis on renal biopsy Right sided monoparesis Unilateral optic atrophy (secondary to previous optic neuritis)	ANA Anti-dsDNA Anti-RNP Anti-Ro/SSA	CS TPE CTX	AZA MMF	2	ON Right sided monoparesis	LETM C3-T1 cen-tral lesion	Normal intracranial appearances	Y	CS TPE CTX	AZA MMF	Re-lapse

Table 1 (continued)

P	A1	G	Clinical features of SLE	Positive anti-bodies	Therapy for SLE		A2	Clinical features of NMOSD				Therapy for NMOSD		
					Induction therapy	Mainte-nance therapy		Phenotype	Spine MRI	Brain MRI	Positive anti-AQP4	Acute therapy	Preventive therapy	Out-come
6 [36]	10	F	Optic neuritis (ON)	ANA Anti-dsDNA	CS	AZA MTX	10	ON TM	LETM C1-C5 central lesion	Abnormal signal right temporal cortex and amigdala and left thalamus and cervi-comedullar junction	Y	CS	ZAZ MTX	Re-lapse
7 [36]	12	F	Vasculitic rash Anaemia Lymphopenia Thrombocytopenia Paresthesias with arms and legs weakness Respiratory failure	ANA ENA	CS TPE IVIG	Rituximab	12	Paresthesias with arms and legs weakness	LETM C1-T1 central lesion	Single non-specific white matter lesion in the right frontal lobe	Y	CS TPE IVIG	Rituximab	CR
8 [37]	16	F	Arthritis Fever Malar rash, Pleuritis Thrombocytopenia	ANA anti-Ro/SSA anti-La/SSB aPL	CS CTX IVIG,	AZA	16	TM	LETM	Normal	Y	CS CTX IVIG	AZA	PR
9 [37]	10	F	Oral ulcers Malar rash Thrombocytopenia Leukopenia Lymphopenia Hypocomplementemia	ANA Anti-dsDNA aPL ACA ACPA	CS CTX	MMF	10	ON ACS	LETM	B, BS	Y	CS CTX	MMF	CR
10 [38]	16	F	NA	ANA Anti-dsDNA	NA	AZA	8	ON Myelitis	LETM	NA	NA	CTX	MP AZA	CR

A1: Age at SLE diagnosis (y), A2: Age at NMOSD diagnosis (y), ACA: anti-centromere antibodies, ACPA: anti-citrullinated peptide antibodies, ACS: acute cerebral syndrome, ANA: antinuclear antibodies, aPL: antiphospholipid antibodies, AQP4: aquaporin 4, AZA: azathioprine, B: brain, BS: brainstem, CR: complete remission, CS: corticosteroids, CTX: cyclophosphamide, dsDNA: double-stranded DNA, ENA: extractable nuclear antigens, G: gender, HCQ: hydroxychloroquine, LETM: longitudinally extensive transverse myelitis, IVMP: intravenous pulse methylprednisolone, MAS: macrophage activation syndrome, MMF: mycophenolate mofetil, MP: methylprednisolone, NA: not available, ON: Optic neuritis, P: patient, PR: partial remission, RF: rheumatoid factor, RNP: ribonucleoprotein, TM: transverse myelitis, TPE: therapeutic plasma exchange

LETM was found by spine MRI in all patients. Acute TM manifests with motor, sensory, and autonomic symptoms of rapid progression with catastrophic outcomes, and LETM refers to a rare and devastating type of TM [41]. However, patients with LETM detected by spine MRI had no severe neurological symptoms or mild clinical evidence of myelitis [35–38], which has also been reported in other studies [41, 42].

The vision of our patient recovered after acute treatment, which included IVMP, TPE and IVIG. Among the other nine patients in the study, four with NMOSD achieved complete remission, two achieved partial remission, and two experienced recurrent relapses with LETM. The treatment strategies for SLE coexisting with NMOSD in children are based on extrapolation from studies in adults with NMOSD or SLE coexisting with NMOSD. There is not enough high-quality evidence about the coexistence of NMOSD and SLE in children, so further research on treatment strategies is needed.

SLE and NMOSD are both autoimmune conditions that can affect the central nervous system, leading to a range of neurological symptoms. SLE coexisting with NMOSD represents a rare but clinically significant occurrence in children. Identifying coexisting SLE and NMOSD is imperative, as treatment differs, and inappropriate treatment can lead to irreversible and severe neurologic outcomes. Pediatricians should consider testing for AQP4-IgG and MOG-IgG in children with SLE who have neurologic symptoms and lesions as shown by brain and spine MRI.

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Author contributions
All authors participated in the design of the review; Rong-xuan Hu reviewed the case and drafted the manuscript; Guo-min Li revised the manuscript; All authors read and approved the final manuscript.

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Ethics approval and consent to participate
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Competing interests
The authors declare that they have no competing interests.

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