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CASE REPORT

AQP4+ NMOSD, MDA5+ Clinically Amyopathic Dermatomyositis and sHLH in a Pediatric Patient: A Case Report and Literature Review

Zhanwei Zhang[1,2,*], Zhangqian Xiao[1,2,*], Fang He[1,2], Fei Yin[1,2], Jing Peng[1,2], Xiaolu Deng[1,2]

[1]Department of Pediatrics, Xiangya Hospital, Central South University, Changsha, 410000, People's Republic of China; [2]Clinical Research Center for Children Neurodevelopmental Disabilities of Hunan Province, Xiangya Hospital, Central South University, Changsha, 410000, People's Republic of China

*Zhanwei Zhang and Zhangqian Xiao contributed equally

Correspondence: Xiaolu Deng, Email dengxiaolu1019@csu.edu.cn

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a rare central nervous system (CNS) autoimmune disorder. It is associated with other autoimmune disorders, which included dermatomyositis in rare conditions. Type I interferon (IFN) has been considered a common link between the two diseases. Furthermore, secondary hemophagocytic lymphohistiocytosis (sHLH) results from overactivation of the immune system and is also associated with autoimmune disorders. This study aims to report a pediatric case of NMOSD overlapping with dermatomyositis, who also developed sHLH, and to summarize all similar cases for expanding the clinical spectrum and treatment outcomes of multi-systemic autoimmune overlap syndromes in children.

Case Presentation: An 8-year-old girl presented with fever, headache, change of consciousness, vomiting, blurred vision, rash, difficulty urinating and neck and back pain. Based on the history, physical examination, and ancillary investigations, the preliminary diagnosis is NMOSD, dermatomyositis, and secondary hemophagocytic lymphohistiocytosis. After aggressive immunotherapy (including intravenous methylprednisolone, intravenous immunoglobin, rituximab and tacrolimus), she fully recovered and remained relapse-free at last follow-up.

Conclusion: NMOSD overlapping dermatomyositis is a rare autoimmune condition with uncertain pathological mechanism. Dermatomyositis should be considered when symptoms such as rash occur in the context of NMOSD. sHLH results from over-activation of the immune system. Aggressive immunotherapy is recommended for better prognosis.

Keywords: neuromyelitis optica spectrum disorder, dermatomyositis, hemophagocytic lymphohistiocytosis, case report

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disorder of the central nervous system (CNS), which is characterized by inflammation of the optic nerve (optic neuritis) and the spinal cord (myelitis). Most patients are positive for aquaporin-4 (AQP-4) IgG antibodies.[1] Previous study by Jarius et al demonstrated that patients of NMOSD with positive AQP-4 antibodies exhibited a clear female predisposition and severe clinical sympotoms [2] Due to abnormal overactivation of immune system, NMOSD, especially AQP4 antibody-positive NMOSD, is usually associated with other autoimmune disorders, such as systemic lupus erythematosus and Sjogren's syndrome.[2,3]

Dermatomyositis is a type of idiopathic inflammatory myopathy characterized by skin and muscle involvement, with varied clinical phenotypes and prognoses associated with different antibody profiles.[4] As mentioned above, AQP4 antibody-positive NMOSD tends to co-exist with other autoimmune disorders. In rare conditions, NMOSD co-exists with dermatomyositis, especially anti-MDA5 antibody positive, which was considered to be correlated with upregulation of type I interferons.[5–8]

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Hemophagocytic lymphohistiocytosis (HLH) is characterized by overactivation of immune system and involvement in multiple organs and divided into two categories by etiology: primary or secondary.[9] Rheumatic diseases, such as dermatomyositis, could be associated with secondary hemophagocytic lymphohistiocytosis (also known as macrophage activation syndrome) with uncertain mechanism.[10]

It is rare and fatal that these three autoimmune disorders coexist. Besides, dermatomyositis with atypical rash was difficult to consider in the context of NMOSD. In this study, we reported a pediatric case of NMOSD and dermatomyositis, who also developed sHLH, and summarized all related cases for expanding the clinical spectrum and treatment outcomes of multi-systemic autoimmune overlap syndromes in children.

Case Presentation

A previously healthy 8-year-old girl presented with recurrent fever, headache, change of consciousness at the onset of the illness, and later progressed to vomiting and blurred vision in the left eye. Red rash is also noted around cheek (Figure 1A). She was then referred to our hospital after no response to antipyretic and antibiotic therapy. After admission, recurrent fever, headache and change of consciousness continued. She then developed blurred vision in the right eye, difficulty urinating, neck and back pain and rash on the palm (Figure 1B). No muscle weakness was mentioned. No relevant family history. Hepatosplenomegaly was noted during physical examination. The routine blood test was unremarkable except for elevated triglycerides (5.52 mmol/L). Muscle enzyme analysis demonstrated no abnormality. Rheumatology test and tumor markers were also unremarkable. Serum ferritin is markedly elevated at >20,000 ng/mL (reference range: <400 ng/mL). Soluble CD25 is also significantly elevated at 22,171 pg/mL (reference range: <6,400 pg/mL). Serous Epstein-Barr virus (EBV) DNA copies detected by polymerase chain reaction were slightly elevated. Routine cerebrospinal fluid (CSF) analysis is within normal limits. Brain magnetic resonance imaging (MRI) demonstrated lesions first in the right thalamus, with subsequent lesions appearing in the corpus callosum while no abnormalities were observed in optic nerves (Figure 2A and B). Spine MRI showed lesion spanning more than three vertebral segments (Figure 2C and D). Based on the patient's history and the above ancillary investigations, the leading diagnostic considerations were neuromyelitis optica spectrum disorder (NMOSD) and secondary hemophagocytic lymphohistiocytosis. Serum anti-aquaporin-4 (AQP4) antibody screening was positive (titer: 1:100) while anti-myelin oligodendrocyte glycoprotein (MOG) antibody screening was negative.

Dermatomyositis was still under consideration despite atypical skin rash. MRI of the thighs suggests edema in the bilateral obturator externus and obturator internus muscles (Figure 2E and F). Dermatomyositis antibody panel was performed, which included anti-Mi-2α, anti-Mi-2β, anti-TIF1γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-HMGCR and

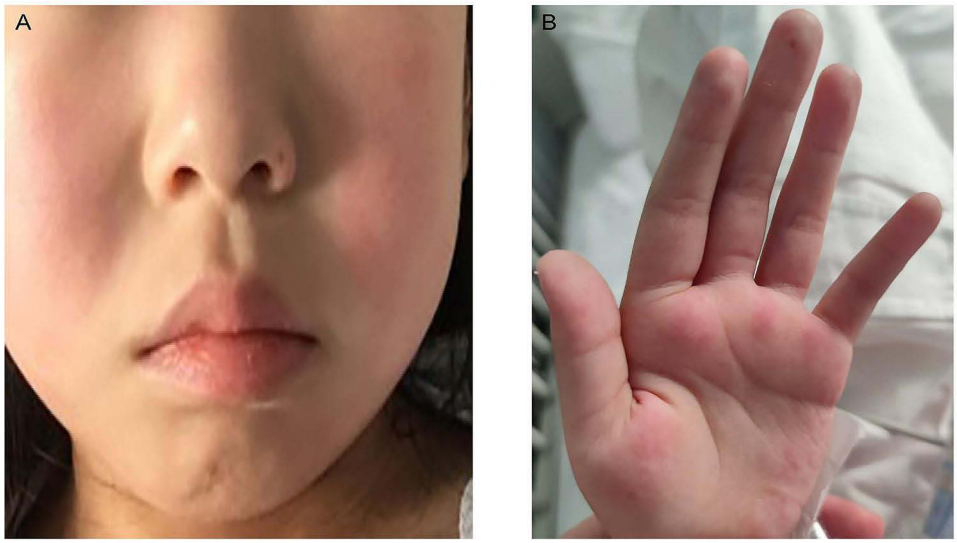

Figure 1 Skin rash of the patient. (**A**) Red rash around cheek of the patient. (**B**) Red rash on the palm on the patient.

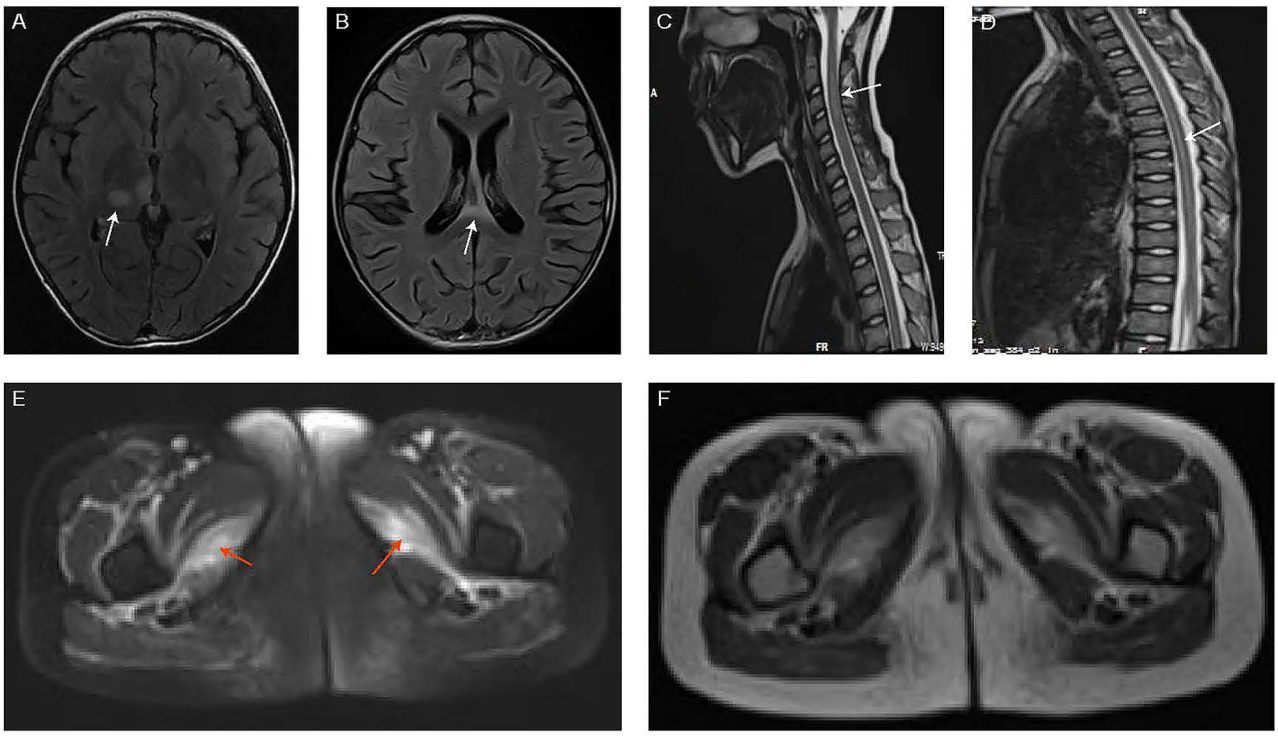

Figure 2 MRI of the patient. (**A** and **B**) Brain MRI of the patient, T2 fluid attenuated inversion recovery (FLAIR) sequence. (**A**) Lesions on the right thalamus (white arrow). (**B**) Lesions on the corpus callosum (white arrow). (**C** and **D**) T2 sequence of spine MRI of the patient, showing longitudinally extensive lesions (white arrows). (**E** and **F**) Thighs MRI of the patient, demonstrating bilateral abnormal signals (red arrows). (**E**) Short tau inversion recovery sequence. (**F**) T2 sequence.

anti-SRP antibodies. The screening was positive for anti-MDA5 antibody (titer: 1:300). Clinically amyopathic dermatomyositis was considered. Chest computed tomography (CT) revealed bilateral pulmonary lesions (Figure 3A and B). Next generation sequencing of bronchoalveolar lavage fluid revealed no pathogens. Connective tissue diseases related organizing pneumonia was considered. No malignancies were found.

Immunotherapy was then initiated, which included intravenous methylprednisolone (IVMP, 10mg/kg/day, 3 days) pulse therapy, followed by a sequential oral prednisone taper, intravenous immunoglobulin (IVIG, 2g/kg), and rituximab (total 1 g, 500 mg per dose, two does, 14days interval). All symptoms except rash have resolved after immunotherapy and she was discharged. Tacrolimus was added to sustain the therapeutic efficacy of immunotherapy. After two years of treatment with tacrolimus and follow-up, rash gradually resolved and no new symptoms occurred with no adverse drug reaction. Serum anti-AQP4 antibody turned negative while anti-MDA5 antibody was still positive with the titer decreased to 1:32. No lesions were seen on brain and spinal MRI. Chest CT revealed improvement of the pulmonary lesions (Figure 3C and D). The timeline was demonstrated in Figure 4.

Discussions

In this study, we reported a pediatric patient diagnosed NMOSD overlapping dermatomyositis who fully recovered after aggressive and long-term immunotherapy. Besides, we summarized clinical features and outcome in patients with NMOSD overlapping dermatomyositis for better understanding of this rare condition (Table 1).

NMOSD is a rare autoimmune disorder with approximate prevalence of 0.07 to 10 per 100,000 population.[11] NMOSD, especially AQP4 antibody-positive NMOSD, exhibits a gender predisposition of female.[2] NMOSD typically occurs in middle age and cases constitute 3–5% of total NMOSD cases.[12] Compared to adult patients, pediatric NMOSD patients with positive antibodies seem to have a higher proportion of MOG antibody positivity than AQP-4 antibody positivity.[13] However, MOG antibody was negative in the two pediatric patients among our summarized cases. Meanwhile, brain lesions are more common in pediatric NMOSD patients than adult patients.[14] In cases we summarized, all patients were anti-AQP4 antibody positive (including pediatric patients) and demonstrated typical symptoms of

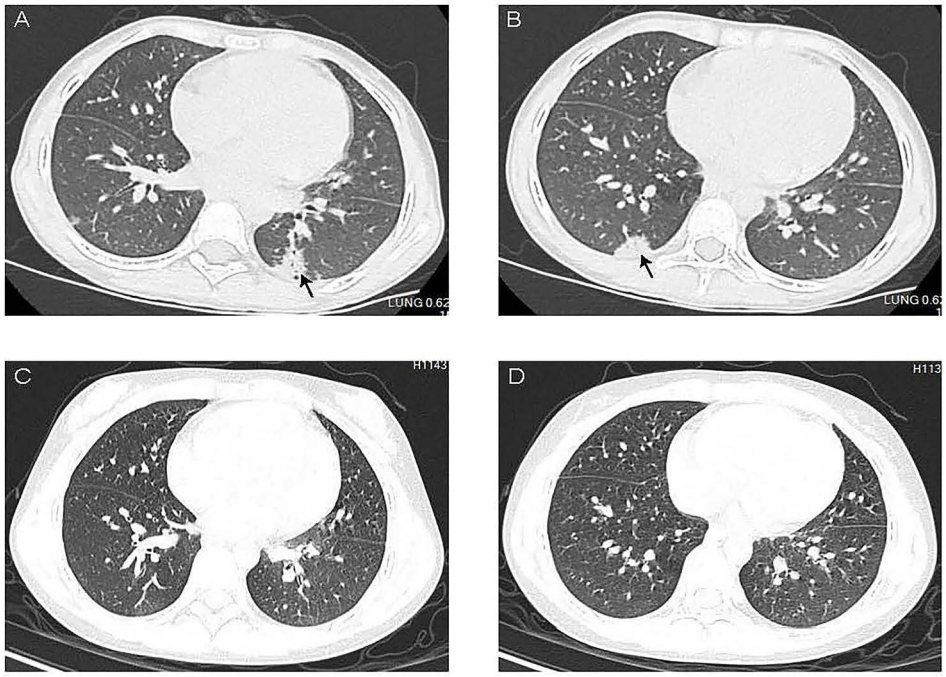

Figure 3 Chest CT of the patient. (**A** and **B**) Chest CT of the patient at first time, showing bilateral pulmonary lesions (black arrows). (**C** and **D**) Chest CT of the patient after immunotherapy with significant improvement.

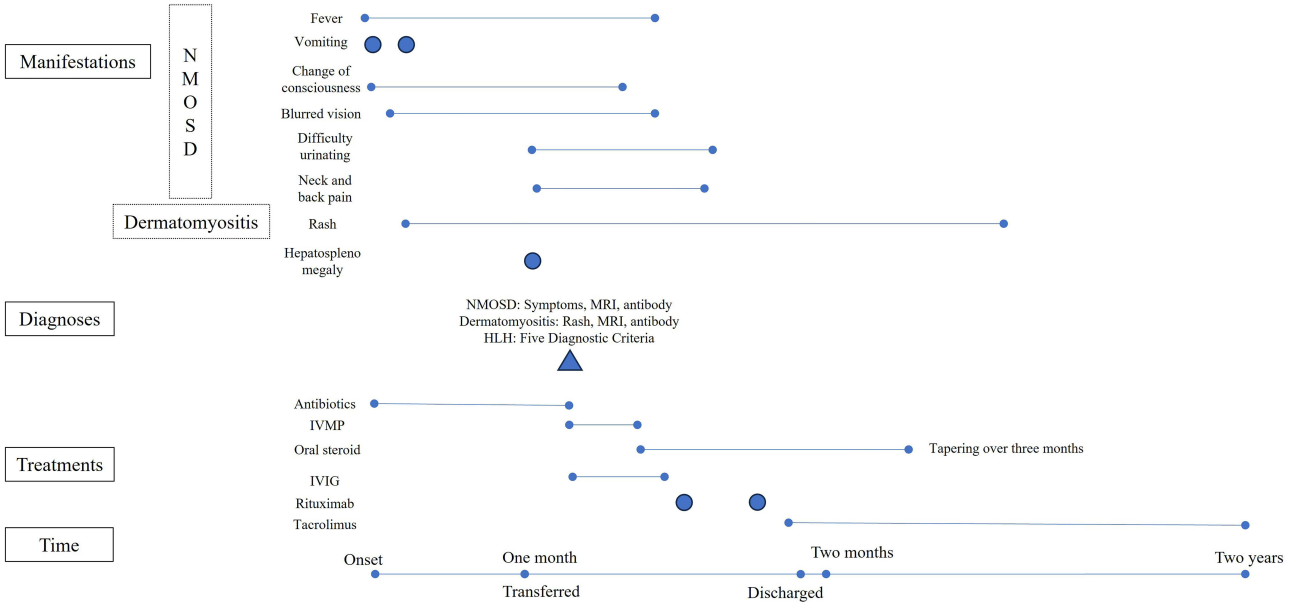

Figure 4 Clinical course diagram of the patient. This figure shows the changes in clinical symptoms, diagnosis, treatment, and prognosis of this patient.

NMOSD. Our pediatric patient presented with encephalopathy accompanied by changes on brain MRI and another pediatric patient from one previous study presented with a demyelination lesion without encephalopathy (Table 1).

Dermatomyositis is a type of idiopathic inflammatory myopathy that is more common than any other types of idiopathic inflammatory myopathy in childhood.[15] In cases summarized, most of them (4/6) were anti-MDA5 antibody positive. All of them presented with cutaneous manifestations while our patient showed atypical rash. But myositis antibody, chest CT and thighs MRI provided further evidence. Two patients were considered clinically amyopathic

Table 1 Literature Review of NMOSD Overlapping with Dermatomyositis

	Case1[5]	Case2[6]	Case3[7]	Case4[8]	Case5[9]	Case[6]
PMID	25595259	33262991	38948240	25766462	31208812	This case
Age of onset	40y	35y	17y	60y	12y	8y
Gender	Female	Male	Male	Female	NA	Female
Clinical presentations	Fatigue, joint pain, rash (heliotrope rash, Gottron's patches, shawl sign, Samitz's sign), back pain, extremity weakness, and urinary retention	Urinary difficulty, decreased visual acuity, paresthesia, cough, joint pain and morning stiffness, rash (erythematous or purpuric patches), dyspnea, paraplegia	Rash (Gottron's patches, mechanic hands, and shawl sign), joint pain and morning stiffness, alopecia, weight loss, heart palpitations, dry mouth, fatigue, extremity weakness, abdominal pain, and inability to urinate	Diarrhea, paresthesia, fecal and urinary incontinence, cutaneous lesions (Gottron's papules, heliotrope rash), weight loss, painful edema of bilateral hands, nonproductive cough and multi joint arthralgias	Muscle weakness, difficulty urinating, rash (Manicure sign, Gottron's signs), joint pain, weight loss, tetraparesis, paresthesia	Recurrent fever, headache, change of consciousness, vomiting, blurred vision, rash (red rash around cheek, rash on the palm), difficulty urinating, neck and back pain
Brain MRI	NA	Retrobulbar neuritis of the right optic nerve	Normal	NA	A demyelination lesion by the occipital horn of the left lateral ventricle	Lesions in the right thalamus and the corpus callosum
Spine MRI	Longitudinally extensive transverse myelitis	Longitudinally extensive transverse myelitis	Longitudinally extensive transverse myelitis	Longitudinally extensive transverse myelitis	Longitudinally extensive transverse myelitis	Longitudinally extensive transverse myelitis
Anti-AQP4 antibody	Positive	Positive	Positive	Positive	Positive	Positive
Muscle examination	EMG: severe myopathy Biopsy: atrophy and structural changes of the muscle fibers	Muscle enzyme: elevated MRI: asymmetric and patchy T2-hyperintensity in hip and thigh muscles	Muscle enzyme: elevated	NA	EMG: normal Muscle enzyme: normal	MRI of the thighs: edema in the bilateral obturator externus and obturator internus muscles
Myositis antibodies	Anti-MDA5 antibodies	Anti-MDA5 antibodies	Anti-MDA5 antibodies	Anti-MDA5 antibodies	Anti-MDA5 antibodies	Anti-MDA5 antibodies
Pulmonary complications	Interstitial lung disease	Interstitial lung disease	NO	NO	NA	Connective tissue diseases related organizing pneumonia
Malignancies	NO	NA	NO	NO	NA	NO
Immunotherapy	Intravenous steroids, prednisone, plasma exchange, rituximab, Intravenous cyclophosphamide, azathioprine	Intravenous methylprednisolone, deflazacort, prednisone, tacrolimus, rituximab, plasma exchange	Intravenous steroids, prednisone, plasma exchanges, rituximab, methotrexate, Intravenous immunoglobin, hydroxychloroquine	Intravenous methylprednisolone, prednisone, plasma exchanges, rituximab, plaquenil, methotrexate	Intravenous methylprednisolone, oral corticosteroids, rituximab, methotrexate	Intravenous methylprednisolone, prednisone, intravenous immunoglobulin, rituximab and tacrolimus
Outcome	Continued dyspnea	Blindness of the right eye, paraplegia, and bladder dysfunction	Ongoing urinary frequency, erectile dysfunction and a persistent rash	Ambulating with assistance	Fully recovered	Fully recovered

Abbreviations: NMOSD, neuromyelitis optica spectrum disorder; Y, year; MRI, magnetic resonance imaging; NA, not available; EMG, electromyography.

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dermatomyositis. Our patient demonstrated skin rash without myopathy including muscle weakness and elevated muscle enzyme although abnormal signs were observed in thighs MRI, consistent with the proposed diagnostic criteria.[16] Clinically amyopathic dermatomyositis is a common condition and is usually connected to rapidly progressive interstitial lung disease (ILD), especially in patients with positive anti-MDA5 antibody.[17] Three patients (3/6) were found to have ILD which is one of the common complications of anti-MDA5 antibody positive dermatomyositis.[18]

Dermatomyositis has been shown to be associated with hemophagocytic lymphohistiocytosis, likely through multiple hypothetical mechanisms involving immune overactivation.[10] Dermatomyositis-related sHLH occurs mainly in juvenile dermatomyositis and MDA5+ dermatomyositis, which is consistent with our case.[19] Dermatomyositis-related sHLH can be fatal with on-admission disease activity, acute exacerbation of interstitial lung disease and infection being risk factors.[10]

As mentioned above, NMOSD can co-exist with dermatomyositis in rare conditions, the specific mechanism of which remains to be elucidated. MDA5 plays an important role in viral recognition and further activates immune response which includes Type I interferon (IFN).[5] Type I IFN involves in abnormal production of antibody in anti-MDA5 antibody positive dermatomyositis and was observed to be positively associated with titers of anti-MDA5 antibody.[20] Previous study showed that IFN therapy worsened NMOSD.[21] Existing evidence suggested that IFN-I plays a pathogenic role in NMOSD by possible mechanisms of increasing AQP4 antigen-specific autoreactive T cells and activation of microglia.[21,22] Therefore, Type I interferon can be intersection of NMOSD and dermatomyositis. Besides, Epstein-Barr virus was detected in our case which could be the trigger and also a common cause of hemophagocytic lymphohistiocytosis. We hypothesized that in our case, EBV triggered an abnormal immune cascade, inducing a series of autoimmune diseases.

Given that NMOSD, dermatomyositis (especially anti-MDA5 antibody positive in overlapping cases) and sHLH could lead to poor outcomes, early and aggressive immunotherapy is recommended.[18,23,24] Corticosteroids are normally first-choice immunotherapy, but they are sometimes ineffective in NMOSD and MDA5. Intravenous immunoglobulin, plasma exchange and combination of other immunosuppressants could be appropriate choices.[18,25] Production of autoimmune antibodies is the core of NMOSD and anti-MDA5 antibody positive dermatomyositis; therefore, depletion of B cells is considered a significant strategy. Previous studies showed that after failure of steroids and immunosuppressants, anti-MDA5 antibody positive dermatomyositis patients benefited from rituximab, which led to improvement in both rash and ILD.[26] Strategy of using rituximab as first-line treatment prevented clinical relapses in pediatric NMOSD cohort, which further indicates important roles of rituximab.[23] Rituximab also demonstrated potential effect in HLH.[27] One case with MDA5+ dermatomyositis and sHLH was treated with IVMP, rituximab and azathioprine and then fully recovered.[28] We applied immunotherapy including IVMP, IVIG and rituximab in acute phase and maintained long-term therapy to prevent relapse, providing a pediatric example for overlapping autoimmune diseases. In cases summarized, all patients received aggressive immunotherapy which included rituximab. Two pediatric patients had favorable outcomes while one adolescent and three adults still suffered from pulmonary or neurological sequela. It remains unclear whether this prognostic difference is due to age, follow-up duration, or treatment conditions. A recent real-world study revealed that no recurrence was observed in AQP4-positive patients after eculizumab treatment. Eculizumab also demonstrated significant superiority in treating AQP4-positive patients who had previously failed rituximab therapy, providing further choices of immunotherapy.[29]

Limitations

This study has several limitations. First, the single-case design precludes generalizability of the treatment outcomes. Second, the concurrent use of steroids, IVIG, and rituximab makes it impossible to isolate the effect of any single drug. Third, although two-year follow-up data are valuable, the long-term safety of tacrolimus in this pediatric population has not been established.

In literature review, the number of such patients is extremely limited, more detailed investigations are needed regarding the age of onset, gender differences, clinical phenotypes, and prognosis. Additionally, whether there are differences in prognosis between adults and children has not yet been fully clarified.

Patient Perspective

The guardians of the patient thought the patient benefited from thorough examination and aggressive treatment.

Conclusions

In conclusions, NMOSD overlapping dermatomyositis is a rare autoimmune condition with uncertain pathological mechanism. Dermatomyositis should be considered when symptoms such as rash (typical or atypical) occur in the context of NMOSD. sHLH results from overactivation of the immune system which should be closely monitored when related manifestations present. Aggressive immunotherapy, including rituximab, is recommended for better prognosis.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Xiangya Hospital of Central South University and conducted in accordance with the ethical standards outlined in the Declaration of Helsinki (Number 202307148-2). Written informed consent was obtained from the legal guardians of the patient. This study adhered to CAse REports (CARE) guidelines (https://www.care-statement.org/).

Consent for Publication

The parents of the patient signed the Institutional Informed Consent for the participation and the publication of their children's individual case details for scientific purposes.

Author Contributions

Zhanwei Zhang: Conceptualization, Data curation, Formal analysis, Writing – original draft; Zhangqian Xiao: Data curation, Formal analysis, Writing – original draft; Fang He, Fei Yin: Supervision, Validation; Jing Peng: Supervision, Validation, Funding acquisition; Xiaolu Deng: Supervision, Validation, Funding acquisition, Writing – review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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