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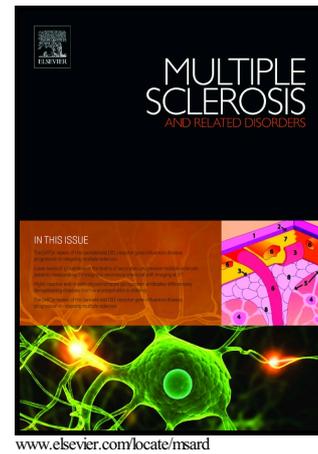
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Author's Accepted Manuscript

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B cell depleting therapy for multiple sclerosis overlapping with neuromyelitis optica spectrum disorder

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Abstract

Multiple sclerosis and neuromyelitis optica spectrum disorder are currently thought to be independent entities. Some patients display intermediate manifestations that fit the criteria for both diseases without positive relevant serobiomarkers. An overall standard and consensus for the diagnosis and treatment of these overlapping patients have not been reached. We describe a patient with frequently relapsing demyelinating episodes and repeatedly adjusted treatment regimens due to diagnostic difficulties. This case did not respond adequately to glucocorticoid plus azathioprine or to interferon. Benefits were finally obtained by using rituximab, an anti-CD20 specific monoclonal antibody targeting B cells. Treatments targeting B cell mediated humoral immunity such as rituximab, may be a safe and appropriate choice for these challenging demyelinating

cases, especially in Asian population.

Keywords

multiple sclerosis; neuromyelitis optica spectrum disorder; demyelination; overlapping; rituximab

1. Introduction

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) have been recognized to be two different disease entities. Diagnosis mainly relies on clinical criteria based on symptoms and imaging findings. Oligoclonal bands (OCB) in cerebral spinal fluid is one of the hallmarks of MS, and similarly aquaporin 4 antibodies (AQP4-IgG) are regarded as a biomarker specific to NMOSD. There are significant differences between the first-line treatments used for the two diseases, and their prognoses are also different, making accurate early diagnosis critical.

A practical difficulty often encountered is that some patients display atypical overlapping symptoms, lacking positive serobiomarkers, making a precise differential diagnosis challenging. This article presents a typical case of MS overlapping with NMOSD, and explores the diagnostic and treatment regimens available for these patients.

2. Case

Half a year postpartum, a 35-year old female patient displayed abnormal sensation in rear shoulder, arms and legs, paraplegia, as well as constipation and dysuria in July 2015. The responsible lesions were identified in the cervical and thoracic spinal cord. Although asymptomatic, multiple brain lesions and bilateral increased optic nerve signal were observed (Fig.1a-f). Results of routine cerebrospine fluid test were non-specific. OCB, AQP4 antibodies, myelin oligodendrocyte glycoprotein antibodies (MOG-IgG) and systemic rheumatoid immune index were all negative. Methylprednisolone pulse therapy was administered for 5 days, followed by gradually tapering oral steroids to a lower maintenance dose. However, the patient experienced gradually worsening mild numbness and stiffness in the upper right limb and mild weakness in the lower right limb in November 2015. A diagnosis of NMOSD was made and 50 mg qd azathioprine (AZA) was added. In December 2015 and January 2016, the patient experienced another two episodes. The AZA dose was

increased to 50 mg bid. In March 2016, the patient experienced vertigo, ataxia, and nuclear facial sensory disturbance on the left side. The symptoms were due to a lesion in the left middle cerebellar peduncle (Fig.1 g-i). The diagnosis was revised to MS. Oral steroids and AZA were discontinued and treatment changed to standard interferon β -1b (Betaferon, Bayer) from 25 April to 20 September. The patient experienced another three episodes during this period. The use of interferon β -1b was discontinued due to poor efficacy and pronounced depression in the patient. On October 11th, the patient experienced dizziness, tinnitus in the left ear and weakness in both lower limbs; these symptoms exacerbated, leading to paralysis and sensory loss in the lower limbs and bed-ridden. Multiple lesions were identified in the spinal cord (Fig.1 j-k). The patient was hospitalized for a total of 127 days in the one year and three months since disease onset. Treatment was then changed to 1000 mg (subdivided into 2 infusions given within half a month) rituximab (Roche) IV every 6 months in November 2016. The patient only experienced one mild relapse in March 2017, which manifested as weakness in the right leg. Disability on the Expanded Disability Status Scale and its relationship to treatment is shown in Fig.2.

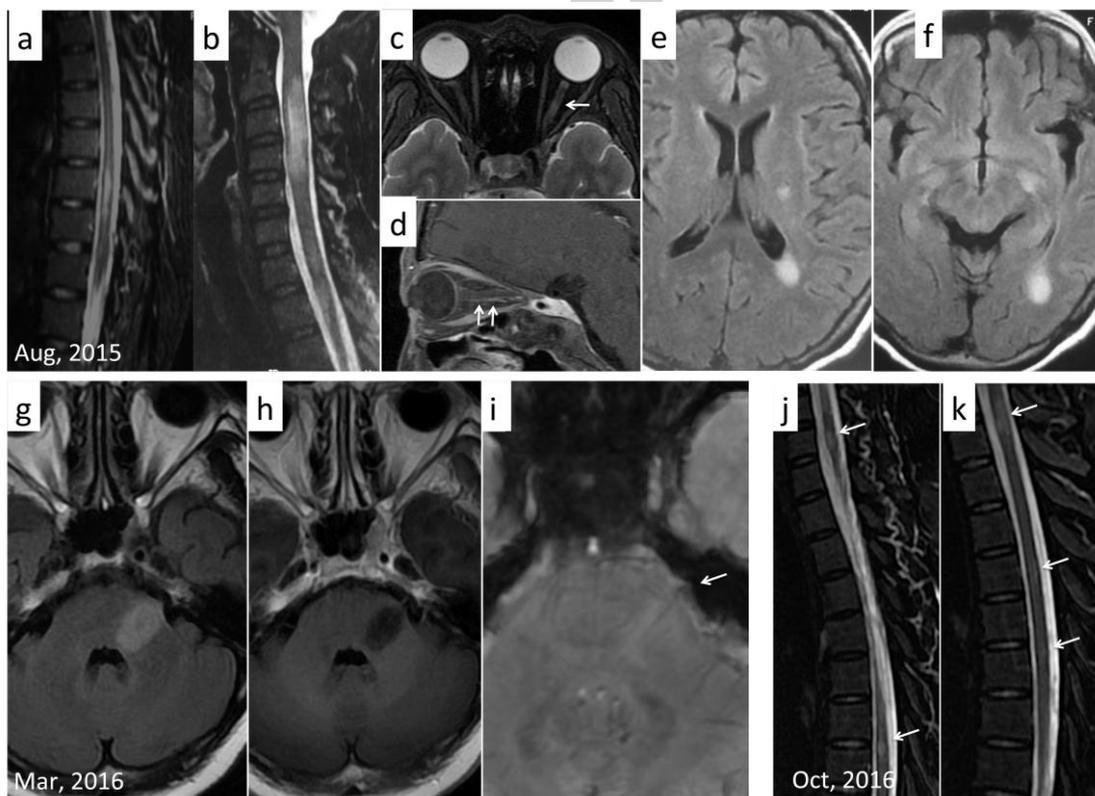


Fig. 1 Magnetic resonance imaging of the patient. a-f First onset of the disease.

Spinal MRI indicated myelitis affecting the cervical and thoracic spine. Central canal dilatation of thoracic cord was observed. T2-weighted MRI images showed abnormal high signal in the left optic nerve, as well as optic nerve surface enhancement (arrows). Multiple lesions were observed in the brain. g-i The 5th episode occurred due to a lesion in the left middle cerebellar peduncle, which was T1 black hole. The SWI sequence showed a lesion surrounding the central veins (arrow). j-k In October 2016, lesions in the spinal cord were particularly short-segmented after interferon discontinuation (arrows).

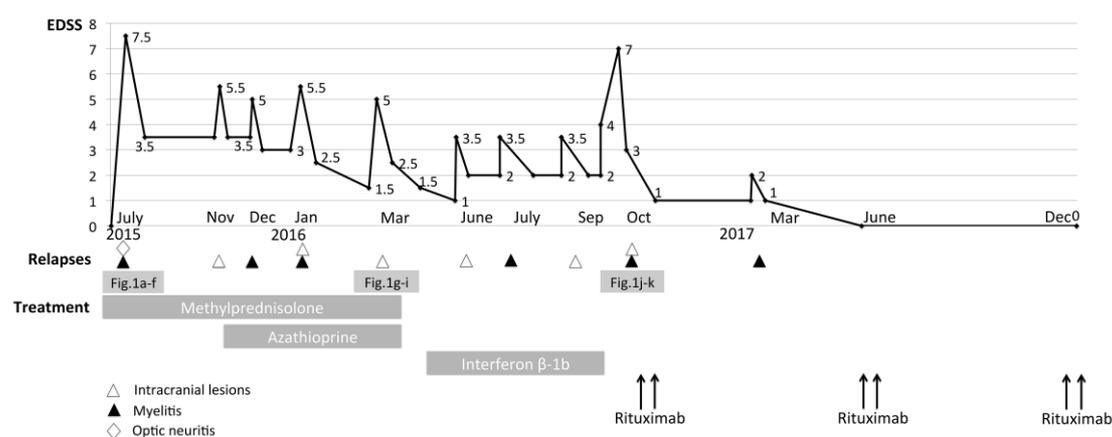


Fig. 2 Expanded Disability Status Scale (EDSS) and adjustments made to the treatment regimen since the onset of the disease.

During the disease activity, abnormal thyroid function was detected and postpartum thyroiditis was considered. Thyroid function indicators gradually returned to their normal ranges during follow-up. The patient was also a hepatitis B virus carrier treated with the antiviral Entecavir 0.5 mg qd.

This study was approved by the Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from the patient to publish her case report.

3. Discussion

The case reported here shared clinical and imaging features of NMOSD and MS. The diagnosis of the case was difficult in part due to the fact that AQP4-IgG, MOG-IgG and OCB were not detected. The initial symptoms were consistent with spinal cord injury. Longitudinally extensive spinal cord lesions and optic nerve lesions affecting over half of the nerve length were observed on MRI. Therefore, the patient

fulfilled the diagnosis of NMOSD with negative AQP4-IgG, though multiple brain lesions were observed with features of oval shape and T1 hypointensity, which are characteristic in MS. MS-like brain lesions occur in approximately 10% of NMOSD patients and should not be considered as solid evidence to exclude the diagnosis of NMOSD [1]. The subsequent symptoms were mainly related to lesions affecting the brainstem and spinal cord. The polyfocal brain lesions were characteristically along the venules on SWI sequence, indicating demyelination caused by inflammation around the central venules. Moreover, the spinal cord lesions were patchy, short-segmented and eccentrically distributed. These features were more consistent with the diagnosis of conventional MS [2].

This case did not respond adequately to glucocorticoid plus AZA or to interferon. Benefits were finally obtained by using rituximab, an anti-CD20 specific monoclonal antibody targeting B cells. In Asian populations, patients with features of NMOSD who also have diagnostic features suggestive of MS are not infrequently encountered. It may be speculated that humoral immunity, rather than T cell-mediated immunity, may play a more important role in their pathogenesis[3, 4].

To date, there are no clinical trials targeting patients with transitional features of both MS and NMOSD; therefore, there are no commonly accepted treatment guidelines or consensus for these patients. Waiting to reach a final diagnosis may be a reasonable choice for some, but frequent clinical relapses occur often and demand early and effective disease-modifying therapy. As humoral immunity is a shared mechanism for NMOSD and MS, treatments targeting humoral immunity may be a safe and appropriate choice[5]. Rituximab and other new B cell depleting agents such as ocrelizumab may have strong disease-modifying effects and are effective in both MS and NMOSD patients [4, 6], suggesting that these drugs may be preferred for the challenging demyelinating case of MS overlapping NMOSD, especially in Asian populations.

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Conflicts of interest

None declared.

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Highlights

- Description of a typical case of MS overlapping with NMOSD
- Humoral immunity as appropriate target for MS and NMOSD overlapping disorders
- B cell depleting agents may be preferred for challenging demyelinating cases.