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CASE REPORT

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Overlapping rheumatoid meningitis with anti-N-methyl-D-aspartate receptor encephalitis: A case report

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Abstract

A 66-year-old woman in treatment for rheumatoid meningitis was found to be positive for anti-N-methyl-D-aspartate receptor (NMDAR) antibodies in the cerebrospinal fluid, and intravenous immunoglobulin improved her psychiatric symptoms. The co-existence of NMDAR antibodies should be considered in cases of poor response to treatments or atypical symptoms in rheumatoid meningitis.

KEYWORDS

anti-N-methyl-D-aspartate receptor encephalitis, intravenous immunoglobulin, intravenous methylprednisolone, rheumatoid arthritis, rheumatoid meningitis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease that can affect multiple organs in addition to the chronic course of destructive arthritis. Peripheral neuropathy has been widely known as a nervous system complication of RA,[1] but recently, with the widespread availability of brain magnetic resonance imaging (MRI), central nervous system (CNS) complications such as meningitis or hypertrophic pachymeningitis have been reported more frequently.

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common type of autoimmune encephalitis caused by antibodies against NMDAR. Recently, there have been increasing reports of anti-NMDAR encephalitis complicating demyelinating diseases of the CNS and autoimmune meningoencephalitis, but there are quite limited case reports of positive NMDAR antibodies in cerebrospinal fluid (CSF) in rheumatic meningitis (RM).[2] Furthermore, there have been no reports in which the presence of NMDAR antibodies in the CSF is thought to be directly related to clinical symptoms. Here, we report a case of overlapping RM with anti-NMDAR encephalitis that was successfully treated with intravenous immunoglobulin (IVIG).

2 | CASE HISTORY/EXAMINATION

A 66-year-old Japanese woman who had been diagnosed with RA 14 years earlier developed persistent low-grade fever from July 2021 and underwent blood tests, but the cause could not be determined. She had been taking prednisolone 4 mg and methotrexate 2 mg for RA, and the disease activity of RA had been stable. In mid-August, she began to have difficulty speaking and showed fluctuations in consciousness. Her consciousness gradually worsened, and she visited our hospital on an emergency basis.

On admission, her temperature was 36.9°C, pulse 86/min, and blood pressure 165/101 mmHg, and general physical examination showed no abnormalities of note. On neurological examination, moderate impairment of consciousness (Glasgow Coma Scale E4V4M6) and strong

psychiatric symptoms including delusions and agitation were evident, but meningeal stiffness was not observed. Blood tests showed mild anemia, with Hb 11.2 g/dL, and inflammatory findings, with CRP 6.52 mg/dL, but liver function and renal function were normal. Anti-cyclic citrullinated peptide antibodies (ACPA) were elevated at 82.8 U/mL. Rheumatoid factor, anti-nuclear antibody, anti-SS-A antibody, and anti-SS-B antibody were all negative. Anti-aquaporin4-antibody was negative measured by both an enzyme-linked immune sorbent assay and a cell-based assay (CBA), and anti-MOG antibody was also negative by a CBA. An electrocardiogram and chest X-ray showed no abnormal findings. Diffusion-weighted imaging and fluid-attenuated inversion recovery imaging of brain MRI showed evident hyperintensity in the leptomeninges of the bilateral cerebral hemispheres (Figure 1, Day 1), but no parenchymal lesions were seen. CSF examination showed a mildly elevated cell count with mononuclear cell predominance (35 cells/μL). CSF protein, β2-microglobulin, and immunoglobulin G (IgG) were elevated at 52 mg/dL, 3.88 μg/mL, and 21.3 mg/dL, respectively. CSF glucose was slightly lower at 50 mg/dL (0.4: divided by serum glucose). The IgG index was 2.77, and oligoclonal bands were positive. ACPA in the CSF was elevated at 12.0 U/mL, and the ACPA-IgG index was also elevated at 8.3 (standard value <1.3).[3]

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Based on clinical symptoms, imaging findings, and CSF findings, the possibility of meningoencephalitis was considered. Although the bilateral meningeal involvement was not necessarily typical, the chronic course and a history of RA suggested RM, and steroid pulse therapy with methylprednisolone (1 g/day for 5 days) was started. Ceftriaxone 4 g/day was also administered until the CSF, and blood cultures proved negative. A total of two courses of steroid pulse therapy were administered and then switched to oral prednisolone. After the start of steroid treatment, her level of consciousness and brain MRI findings gradually improved (Figure 1, Day 20), ACPA in the CSF became negative, and CSF protein normalized (29 mg/dL), but she continued to have severe psychiatric symptoms. After additional evaluation for comorbidities, NMDAR antibodies in the CSF were positive by CBA (titer 1:20). Pelvic MRI and whole-body computed tomography showed no neoplastic lesions, including ovarian teratoma. We consulted a psychiatrist, but her psychiatric symptoms were refractory to psychotropic medications, and IVIG (400 mg/day for 5 days) was additionally started on the 25th day. After IVIG, her psychiatric symptoms improved slowly and resolved; therefore, second-line treatment for anti-NMDAR encephalitis was not required.

4 | OUTCOME AND FOLLOW-UP

Brain MRI at 1-month follow-up showed that the hyperintensity in the leptomeninges had almost disappeared (Figure 1, Day 46). Prednisolone was gradually tapered to 20 mg, and the patient was transferred to a rehabilitation hospital on the 48th day of admission (Figure 2).

5 | DISCUSSION

RM was first reported in 1954 with the demonstration of rheumatoid nodules in the dura mater in autopsy cases,[4] and the term "rheumatoid meningitis" was proposed in

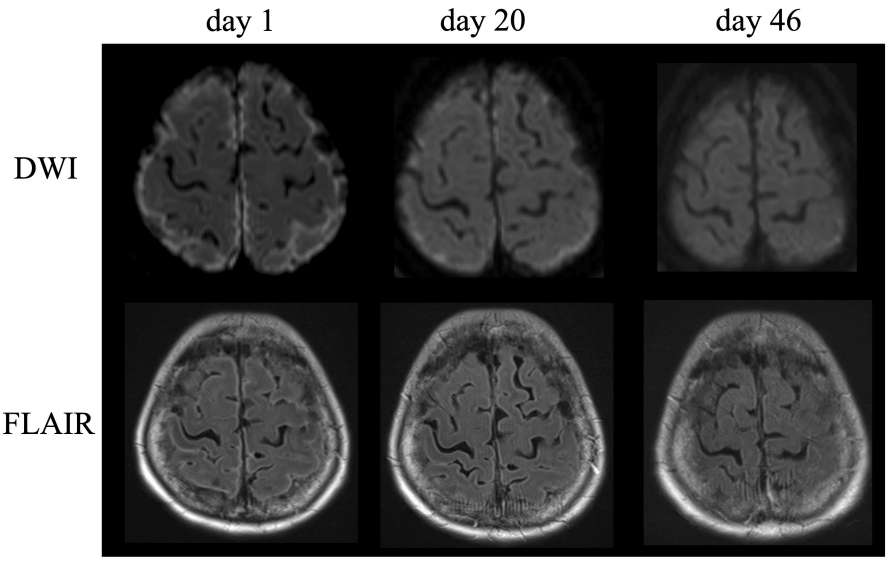

FIGURE 1 MRI of the brain. DWI and FLAIR imaging of brain MRI on admission show obvious hyperintensity in the leptomeninges of bilateral cerebral hemispheres (Day 1). After two courses of steroid pulse therapy, the lesions gradually improve (Day 20), and just before transfer, the hyperintensities in the leptomeninges have almost disappeared (Day 46). DWI: diffusion-weighted imaging, FLAIR: fluid-attenuated inversion recovery.

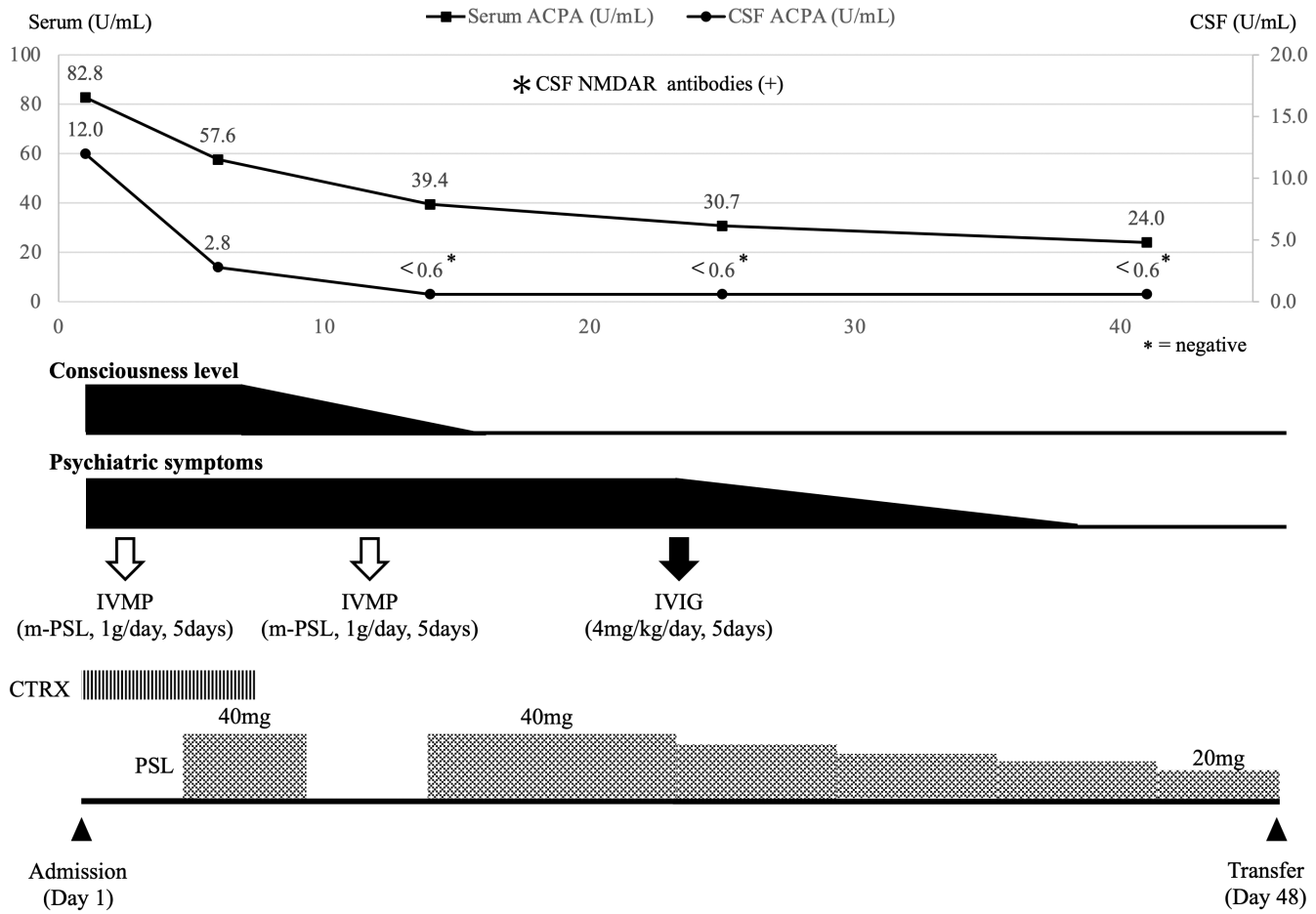

FIGURE 2 Clinical course of the patient. The level of consciousness improves after two courses of steroid pulse therapy, and ACPA in the CSF also becomes negative. However, psychiatric symptoms persist. Additional tests show positive NMDAR antibodies in the CSF, and IVIG improves psychiatric symptoms. Prednisolone is tapered from 40 mg to 20 mg, and the patient is transferred to a rehabilitation hospital at 48 days. ACPA: anti-cyclic citrullinated peptide antibodies, CSF: cerebrospinal fluid, NMDAR: anti-N-methyl-D-aspartate receptor, IVMP: intravenous methylprednisolone, m-PSL: methyl-prednisolone, IVIG: intravenous immunoglobulin, CTRX: ceftriaxone, PSL: prednisolone.

1979.[5] In the majority of cases, the meningeal lesions are unilateral,[6] but bilateral lesions have also been reported, as in the present case. In fact, a review of 35 cases of RM showed that 5 cases had bilateral meningeal involvement.[7] Pathologically, RM is characterized by inflammatory cell infiltration of the meninges and subarachnoid space, rheumatoid nodules, and vasculitis,[8] but it has been reported that rheumatoid nodules are demonstrated on meningeal biopsy in only 42%–56% of patients with RM.[9,10] Recently, it has been reported that elevated ACPA in the CSF and the ACPA-IgG index are useful for diagnosis.[11–13] ACPA is an auto-antibody specific to RA, and intrathecal production of ACPA is thought to be involved in citrullinated protein production in the CNS and B cell infiltration into the CNS.[12] The ACPA-IgG index is calculated as (ACPA in the CSF/ACPA in the serum) / (IgG in the CSF/ IgG in the serum), and an ACPA-IgG index greater than 1.3 indicates increased intrathecal antibody production.[3] It has been reported that calculation of the ACPA-IgG index may increase the sensitivity and specificity of laboratory diagnostics for RM and reduce the need for more invasive meningeal biopsy.[14] ACPA in the CSF and the ACPA-IgG index have been reported to correlate with RM disease activity.[12,13,15] In the present case, the diagnosis of RM was made based on a long history of RA, the fact that infectious pathogens that could cause chronic meningitis were ruled out on examinations, a markedly elevated ACPA in the CSF and the ACPA-IgG index, and rapid improvement in neurological symptoms and MRI findings with the initiation of steroid treatment. ACPA in the CSF decreased rapidly with steroid treatment, and this was also considered compatible with the course of RM after treatment. Meningeal biopsy was not performed because the meningeal lesions were responsive to steroids and gradually shrinking on brain MRI, and also because of the potential invasiveness of the procedure to the patient. On the hand, the strong psychiatric symptoms persisted even after improvement of the neurological symptoms, imaging, and

CSF findings, which was atypical for the course of RM, generally considered to have a good response to treatments.[7] Additional tests showed that NMDAR antibodies in the CSF were positive by CBA, and subsequent treatment with IVIG resulted in improvement of the psychiatric symptoms.

Anti-NMDAR encephalitis is the most common type of autoimmune encephalitis caused by antibodies against NMDAR, and tumors, infections, and systemic autoimmune diseases trigger antibody production.[16] There are reports of positive NMDAR antibodies in systemic autoimmune diseases such as Hashimoto's thyroiditis and systemic lupus erythematosus.[17,18] Recently, there have also been increasing reports of anti-NMDAR encephalitis complicating viral encephalitis and autoimmune diseases of the CNS. Of 51 patients with herpes simplex encephalitis, 27 developed autoimmune encephalitis during the disease, and nine were positive for NMDAR antibodies.[19] There have also been reports of anti-NMDAR encephalitis associated with autoimmune demyelinating diseases of the CNS, which is termed overlapping demyelinating syndrome.[20] Of 691 patients with anti-NMDAR encephalitis, nine (1.3%) were positive for anti-MOG antibody and 9 (1.3%) for anti-aquaporin4-antibody.[20] Moreover, it has been reported that NMDAR antibodies were positive in GFAP astrocytopathy, which presents with autoimmune meningoencephalitis, and in GFAP astrocytopathy patients, 20% (2 of 10) of children and 12.5% (10 of 80) of adults were found to be NMDAR antibodies-positive.[21] The cause of anti-NMDAR encephalitis is unknown, but possible mechanisms such as molecular homology or the release of NMDAR from neurons as a result of viral infection or autoimmune inflammation have been suggested.[19] There is only one case of RM reported to date in which NMDAR antibodies in the CSF were positive.[2] However, in the previous report, the only symptom was paroxysmal weakness of the lower limbs, so the diagnostic criteria for anti-NMDAR encephalitis were not met. In addition, NMDAR antibodies in the CSF were weakly positive (titer 1:1), suggesting that the involvement of NMDAR antibodies in the pathogenesis of the disease is uncertain. It has been reported that psychiatric symptoms occur in 47% (54/112) of patients with RM[10] and about 95% of adults with anti-NMDAR encephalitis.[22] In the present case, since strong psychiatric symptoms persisted even after ACPA in the CSF turned negative, the possibility that NMDAR antibodies were also involved in the pathogenesis as a complication of RM was considered, and a diagnosis of anti-NMDAR encephalitis was made according to the diagnostic criteria.[23] As discussed in the above reports,[19–21] co-exiting NMDAR antibodies should also be considered in infectious and autoimmune inflammatory pathologies of the CNS if the disease course is not monophasic, if the response to standard therapy is insufficient, or if atypical symptoms such as involuntary movements or psychiatric symptoms are also present. Although there are limited reports of the efficacy of IVIG in RM,[2] the present results suggest that IVIG may be effective in patients with RM with positive NMDAR antibodies. However, there have been limited case reports to date, and further cases and research on the frequency of NMDAR antibodies positivity in RM, pathological links, clinical course, and treatment methods are warranted.

AUTHOR CONTRIBUTIONS

Toshihiro Ide: Writing – original draft. **Takeru Kawanami:** Writing – review and editing. **Yoshifumi Tada:** Writing – review and editing. **Makoto Eriguchi:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

All the required information is in the manuscript itself.

PATIENT CONSENT

Written, informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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