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A refractory anti-NMDA receptor encephalitis successfully treated by bilateral ovariectomy and intrathecal injection of methotrexate and dexamethasone: A case report

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Case report

Keywords: Intrathecal injection of MTX and DXM may be beneficial for patients with anti-NMDA receptor encephalitis

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Abstract

Background: Anti-N-methyl-d-aspartate (anti-NMDA) receptor encephalitis is an autoimmune-mediated disease, which is predominant in young female patients with ovarian teratomas. With proper immunotherapy, most of the patients achieve good prognosis. Nevertheless, some patients may be refractory to first and second-line immunotherapy, thus new treatments are required to help these patients. Case presentation: We present a case of anti-NMDA receptor encephalitis with ovary teratoma. After the prompt removal of the teratoma and strong immunotherapy including intravenous methylprednisolone pulse (IVMP), intravenous immunoglobin (IVIG), plasmapheresis, immunoadsorption, intravenous cyclophosphamide, and rituximab, the patient's neurologic status did not improve. Bilateral ovariectomy was then conducted and intrathecal injection of methotrexate (MTX) and dexamethasone (DXM) was given. The patient's neurological symptoms improved dramatically and she achieved a good prognosis after 23 months. Conclusions: For refractory cases of anti-NMDA receptor encephalitis, intrathecal injection of MTX and DXM may be beneficial. More research is required to elucidate the mechanisms of intrathecal treatment.

Background

Anti-N-methyl-d-aspartate (anti-NMDA) receptor encephalitis has recently been reported as paraneoplastic limbic encephalitis, which mainly affects young females with ovary teratomas [1]. Clinical therapy, including first-line immunotherapy (steroids, intravenous immunoglobulin, plasmapheresis), second-line immunotherapy (rituximab, cyclophosphamide), and tumor removal is recommended for the treatment of this condition. With proper therapy, most of the patients achieve good prognosis (modified Rankin Scale, mRS < 2) within 24-month follow up [2]. Nevertheless, about 19% patients may have a poor prognosis following the first and second line treatment.

Ovarian teratomas were reported to be associated with the disease in 58% of the cases [3]. The teratomas contain neuronal cells that result in immunologic sensitization against the NMDA receptors and even small teratomas containing nervous tissue may result in severe complications secondary to anti-NMDA receptor encephalitis [4]. The longest clinical duration of coma in anti-NMDA receptor encephalitis has not yet been reported. Herein, we present a case of anti-NMDA receptor encephalitis with right side ovarian teratoma. The patient was refractory to the first and second line therapy. Bilateral ovariectomy was conducted and intrathecal injection of methotrexate (MTX) and dexamethasone (DXM) was initiated. The patient finally recovered consciousness and a good prognosis at 17 months and 23 months from the onset of the disease, respectively.

Case Presentation

A 27-year old female was transferred to our department following three seizure episodes and loss of consciousness that occurred on Nov 4, 2016 and lasted for one day.

She was admitted at a local psychiatric department for acute psychosis that lasted for 3 days during which she spoke few words, was restless and unwilling to eat. A week before her symptoms appeared, she had cold-like symptoms with a runny nose and low-grade fever between 37-38℃. Her past medical history was not remarkable.

On admission, physical examination revealed that her vital signs were stable and neurological examination based on Glasgow coma scale showed that she had a score of 6 (E1V1M4). Laboratory results and electroencephalogram (EEG) were not remarkable. Cranial MRI with contrast showed mild signal changes in the bilateral hippocampus and left temporal cortex, and local meningeal congestion. Anti-NMDA receptor antibodies were detected in the serum and cerebrospinal fluid (CSF) (1:1000 and 1:100, respectively).

Abdominal ultrasound screening showed a weak liquid echo of the right ovary, and teratoma was highly suspected. Tumor removal was initiated after the diagnosis was made on Nov 5, 2016, and the pathology confirmed the diagnosis of teratoma with nerve tissues inside.

The patient was comatose with persistent facial involuntary movement including lip peristalsis and eyebrow winking, which were treated with a large dosage of anesthetic agents.

After the diagnosis of anti-NMDA receptor encephalitis was made, the first line therapy including intravenous methylprednisolone pulse (IVMP), intravenous immunoglobin (IVIG), plasmapheresis and immunoadsorption was conducted. However, the patient was refractory to all the treatment. Her neurological status did not improve and the titers of anti-NMDA receptor antibodies in both serum and CSF were persistently high (Table 1). Considering the poor reaction to treatment, the second line therapy that included rituximab and intravenous cyclophosphamide was initiated. The patient did not react to this treatment.

Since patient manifested the high titer of antibodies, it made us consider non-visible teratomas of the ovaries. After obtaining the informed consent from the family members, bilateral ovariectomy was conducted on Oct 26, 2017 and the pathology revealed inflammation, while no teratoma was seen.

Immunosuppressant including mycophenolate mofetil (MMF) 0.75g bid was initiated after the failure of the first and second line therapy. Intrathecal MTX 10 mg and DXM 10 mg were given once a week for 5 weeks and the titer of the antibody of CSF gradually decreased (Table 1) and during the follow-up, the titer decreased to 1:10 on April 20, 2018. After the therapy, the patient awoke after 17 months. With 6-month physical therapy, she achieved a good prognosis with the mRS score of 1. During the follow-up, an X-ray examination of the patients' shoulders showed diffused muscular ossification (Figure 1).

Discussion And Conclusion

A large cohort study enrolling 577 patients have found that in most patients with anti-NMDA receptor encephalitis, respond to immunotherapy and second-line immunotherapy is usually effective when first-

line treatments fail. In some patients in this cohort, the recovery took up to 18 months [2]. The patient in our study had a poor response to both the first and second line therapy, which made it a refractory case.

The comorbidity of teratoma and anti-NMDA receptor encephalitis has been widely reported. The incidence varies from 6% to 38% with lower incidence in younger patients [2, 5]. Delayed teratoma development and image invisible teratoma have been previously reported [1, 6]. Zainab *et al.* have described a case of a patient who received bilateral oophorectomy though multiple imaging investigations showed no evidence of teratomas. Ovarian histology confirmed the diagnosis of teratoma with nerve tissues [1]. In our case, at the onset of the disease, the ultrasound revealed a teratoma of the right ovary and tumor removal was conducted within a week of the disease. The unresponsive effect of the treatment made us consider the possibility of non-visible teratomas. Based on the clinical suspicion of tiny teratomas, the patient underwent bilateral ovariectomy. However, the pathology did not show any evidence of teratomas.

Intrathecal injection of MTX and DXM has shown to be beneficial to treat neuropsychiatric systemic lupus erythematosus (NPSLE) patients, particularly those patients who were refractory to traditional therapy or those who had contraindications for IVMP and intravenous cyclophosphamide [7]. The therapy has been widely used in treating NPSLE[8, 9]. A study that evaluated the effect of methylprednisolone combined with MTX and DXM in NPSLE patients and its effect on anti-NMDA receptor subtype NR2a/2b antibody level has reported that after the treatment, positive rates of autoantibodies and anti-NR2 antibody in both NPSLE and non-NPSLE group were significantly decreased, while the negative conversion rate was as high as 61.5%[10]. Based on the encouraging effect of intrathecal injection of MTX and DXM in NPSLE, we tried this therapy in our patient. The neurologic status of our patient improved dramatically after the intrathecal therapy.

MTX is a potent immunosuppressive agent, which cannot penetrate the blood-brain barrier. Intrathecal administration can increase the local concentration and thus enhance the immunosuppressive effect [8]. Nonetheless, intrathecal injection of MTX should be used with caution in anti-NMDA receptor encephalitis. A case report of a young female patient with methotrexate neurotoxicity was worth our consideration. EEG of the young female leukemia patient with a high dosage of intrathecal MTX showed delta brush [11], which has been reported in about 30.3% patients with anti-NMDA receptor encephalitis [12]. NMDA receptor is involved in the pathogenesis of MTX neurotoxicity. MTX interferes with potentially neurotoxic amino acid and neurotransmitter pathways causing accumulation of homocysteine and its metabolites with strong excitatory effect on NMDA receptors [13]. These findings seem paradoxical. We hypothesize that MTX has some effect on NMDA receptors and appropriate dosage may be beneficial for anti-NMDA receptor encephalitis. Further research is warranted to elucidate the underlying mechanisms in intrathecal MTX for patients with anti-NMDA receptor encephalitis.

Another interesting point in this case is that the patient developed severe and diffused muscle ossification. This phenomenon is heterotopic ossification (HO) and is consistent with our experience [14].

Very severe neurologic symptoms, long-term intensive care, muscular spasticity, and mechanical ventilation were probably the cause of HO development in the patient.

Anti-NMDA receptor encephalitis is a newly recognized auto-immune disease. In most patients, favorable prognosis is achieved with the first and second-line immune therapy. In some rare cases, in which patients poorly react to strong first and second-line treatment, intrathecal MTX with DEM may be beneficial.

Abbreviations:

anti-NMDA: Anti-N-methyl-d-aspartate; CSF: cerebrospinal fluid; DXM: dexamethasone; EEG: electroencephalogram; HO: heterotopic ossification; IVMP: intravenous methylprednisolone pulse; IVIG: intravenous immunoglobin; MMF: mycophenolate mofetil; mRS: modified Rankin Scale; MTX: methotrexate; NPSLE: neuropsychiatric systemic lupus erythematosus.

Declarations

Ethics approval and consent to participate

Institutional review board/ethics committee approval was obtained from the Institutional Review Board of the Nanfang Hospital, Southern Medical University.

Consent to publish

Written informed consents were obtained from the patient and her parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

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

Competing interests

The authors declared no conflicts of interest with respect to the research, authorship, funding, and/or publication of this article.

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was responsible for the concept and design of the study. Also, SP revised the manuscript.

Authors' Contributions

DW, YW, ZJ, SW and SP are responsible for concepts and design. YX, KH, YP, HZ and HW are responsible for taking care of the patient. DW and XZ are responsible for data collecting. All authors contributed intellectually. All authors acquired, analyzed, and interpreted the data. The manuscript was prepared by DW and SP. All authors reviewed and made critical revisions to the manuscript.

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Table

Table 1 Clinical treatment and serum and CSF antibody titers of the patient.

Date	Immunotherapy	Serum anti-NMDA receptor titer	CSF anti-NMDA receptor titer	Infections
Nov 5, 2016	Plasma Exchange for 5 days	1:1000	1:100	
Nov 6, 2016	IVMP with 0.5g/d for 5 days and tapered to oral MP 40mg	1:1000	1:100	
Nov 10, 2016	IVIG with 20g for 5 days	1:1000	1:100	
Nov 21, 2016	IVIG with 20g for 5 days	1:1000	1:100	
Dec 1, 2016	Plasma Exchange for 5 days	1:1000	1:100	
Dec 15, 2016	Oral MP 40mg	1:1000	1:100	Septicemia with *Staphylococcus goats*
Dec 22, 2016	IV CTX 0.4g	1:1000	1:100	
Dec 29, 2016	IV CTX 0.6g	1:1000	1:100	
Jan 11, 2017	IVIG with 20g for 5 days	1:1000	1:100	
Jan 13, 2017	IVMP with 0.5g/d for 5 days and tapered to oral MP 40mg	1:1000	1:100	
Feb 17,2017	Immunoadsorption for 5 days	1:1000	1:100	
Mar 7, 2017	Rituximab 100mg Qw for 4 weeks	1:300	1:100	Septicemia with *klebsiella pneumoniae*
Apr 28, 2017	Plasma Exchange for 5 days	1:300	1:100	
May 14, 2017	Plasma Exchange for 5 days	1:300	1:100	
Dec 12, 2017	Mycophenolate mofetil (MMF) 0.75g bid	1:300	1:100	
Dec 26, 2017	IVIG with 20g for 5 days	1:300	1:100	
Dec 26,2017	IVMP with 0.5g/d for 3 days and tapered to oral MP 40mg	1:300	1:100	
Jan 16,2018	Intrathecal therapy with DXM and MTX for 5 times (Once per week)	1:300	1:32	

DXM: dexamethasone; IVMP: intravenous methylprednisolone pulse; IVIG: intravenous immunoglobin; MMF: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate.

Figures

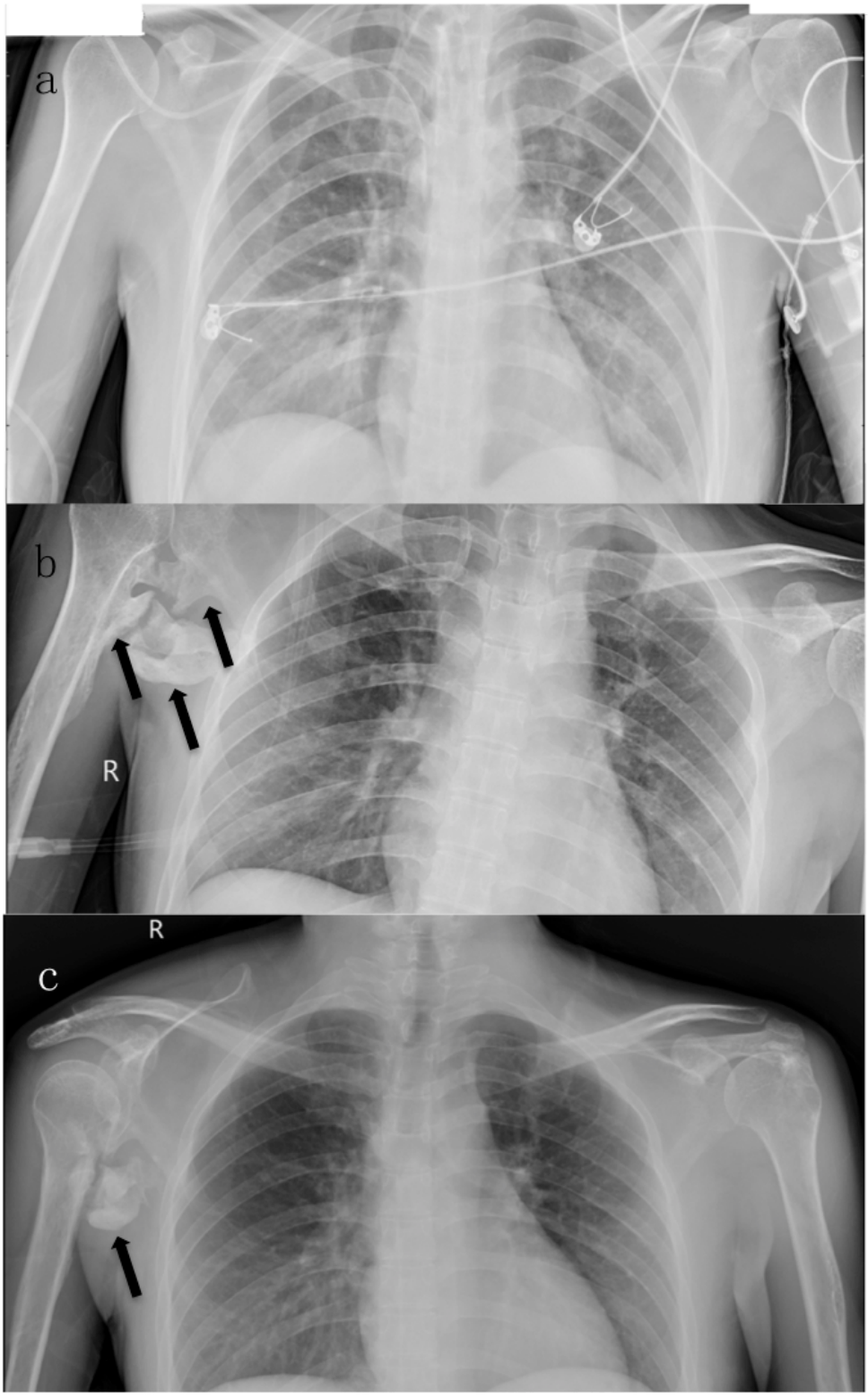


Figure 1

Chest-X-ray examinations of the patient. No significant ossification was observed at the beginning of the disease (Nov 15, 2016) (a). During the disease period (Aug 26, 2018), diffused ossifications were observed in the right scapula and upper humerus (black arrows) (b). With proper physical therapy, the ossifications were decreased (black arrow, Sept 11, 2018) (c).

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