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Case Report

Anesthetic Management and Postoperative Course of a Patient with Anti-N-Methyl-D-Aspartate Receptor Encephalitis Associated with Ovarian Teratoma

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ABSTRACT: A 32-year-old woman complained of fever, hallucinations, and seizures. Based on her symptoms and the presence of an ovarian tumor, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was suspected. Without waiting for specific antibody test results, she underwent emergency laparoscopic salpingo-oophorectomy. The patient received general anesthesia, which was maintained with midazolam, propofol, opioids, and rocuronium. Her anesthesia recovery was uneventful, and she had tracheal extubation after surgery. Postoperatively, her symptoms deteriorated, despite first-line immunotherapy using immunoglobulin, steroids, and plasmapheresis. She required respiratory support for central hypoventilation. As second-line immunotherapy, rituximab and cyclophosphamide were administered, resulting in gradual symptom improvement. Approximately five months after onset, she was discharged in an ambulatory condition. Early tumor resection, combined with immunotherapy, is recommended for anti-NMDAR encephalitis secondary to tumors. Since there are individual differences in the clinical courses of patients with this disease, careful perioperative management is essential.

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KEYWORDS: anti-N-methyl-D-aspartate receptor encephalitis, laparoscopic salpingo-oophorectomy, anesthetic management, postoperative course

Introduction

Dalmau reported, in 2007, about anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, a paraneoplastic syndrome associated with teratoma. Its pathogenesis is auto-antibody production against one of the glutamine receptors, NMDAR.[1] This disease, primarily found in young women, is characterized by memory deficits, psychiatric symptoms, seizures, decreased consciousness, and central hypoventilation. Although the long-term prognosis is generally good, some cases are treatment-resistant. Early tumor resection and immunotherapy are recommended for patients suffering from anti-NMDAR encephalitis associated with tumors.[2] The number of reported anti-NMDAR

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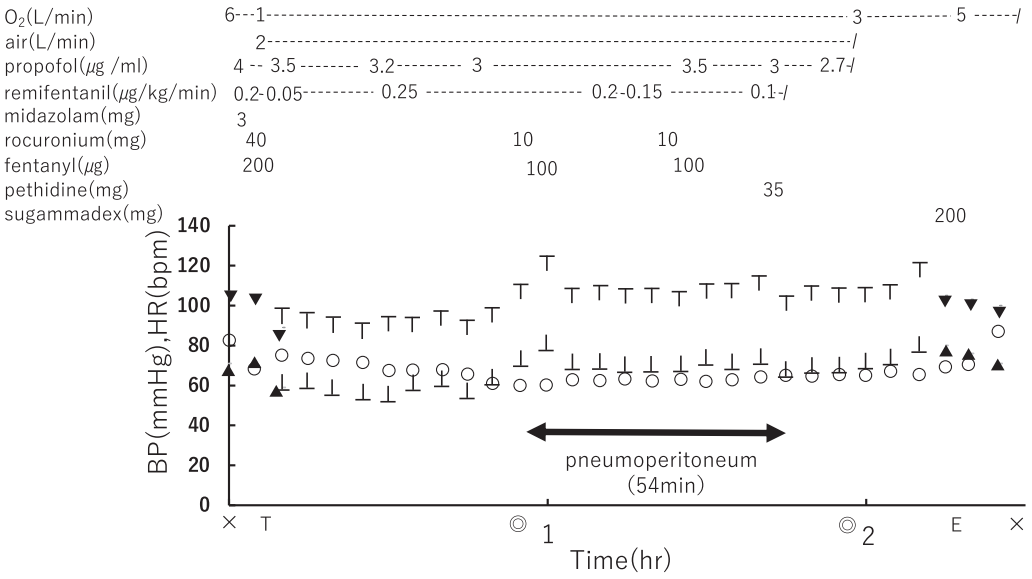

Fig. 1 Anesthetic record

▼/▲: noninvasive systolic/diastolic blood pressure, ┬/┴: invasive systolic/diastolic blood pressure, ○: heart rate, X-X: anesthesia time, ◎: surgery time, T: tracheal intubation, E: tracheal extubation, BP: blood pressure, HR: heart rate

encephalitis cases is increasing, resulting in several anesthetic case reports of tumor resection, gastrostomy for nutritional management, and cesarean section in patients with anti-NMDAR encephalitis.[3–5] The rise in cases suggests that opportunities for anesthetic management in patients with anti-NMDAR encephalitis will increase. However, there are no established guidelines. This case report concerns the perioperative course of a 32-year-old woman with anti-NMDAR encephalitis who underwent laparoscopic ovarian teratoma resection.

Case Report

A 32-year-old woman (150 cm tall, weighing 53 kg) was transferred to the emergency department of our hospital by ambulance 3 d after the onset of visual and auditory hallucinations with frequent seizures, preceded by common cold symptoms. She was immediately admitted to the neurology department. She had previously been diagnosed with ovarian teratoma at the age of 17-years. Computed tomography (CT) of the abdomen indicated a right multilocular cystic ovarian tumor, 63 mm in diameter, with calcification and fat. There were no abnormalities in the left ovary. CT and magnetic resonance imaging scans revealed no organic abnormalities in the brain. Cerebrospinal fluid (CSF) analysis revealed an increased number of cells in CSF. Based on her clinical symptoms and the ovarian tumor, anti-NMDAR encephalitis was suspected. Blood and CSF samples were submitted to another hospital to determine the presence of anti-NMDAR antibodies. Detecting these autoantibodies is important for confirming the diagnosis; however, the test results take about two weeks. Therefore, we decided to perform emergency laparoscopic right salpingo-oophorectomy under general anesthesia on the night she was admitted to the hospital.

The patient was completely conscious just before induction of general anesthesia. Fig. 1 shows her anesthetic record. She had the usual noninvasive intraoperative monitoring, such as electrocardiograph, pulse oximeter, and noninvasive blood pressure. After oxygenation using a face mask, we induced general anesthesia with midazolam (3 mg), fentanyl (200 μg), and propofol (administered at the rate required to achieve an estimated plasma concentration of 4 μg/mL, using a target-controlled infusion pump (TE-371, TERUMO CORPORATION, Tokyo, Japan)). Rocuronium was administered to facilitate tracheal intubation; then, we inserted a 22-gauge needle into her left radial artery for continuous monitoring of arterial blood pressure. General anesthesia was maintained with propofol (estimated plasma concentration of 2.7-3.5 μg/mL), remifentanil (0.1-0.25 μg/kg/min), fentanyl (200 μg) and pethidine (35 mg). A bispectral index was monitored and maintained at approximately 40 during surgery. The laparoscopic inspection revealed no abnormalities of the left ovary. After an uneventful surgery, sugammadex (200 mg)

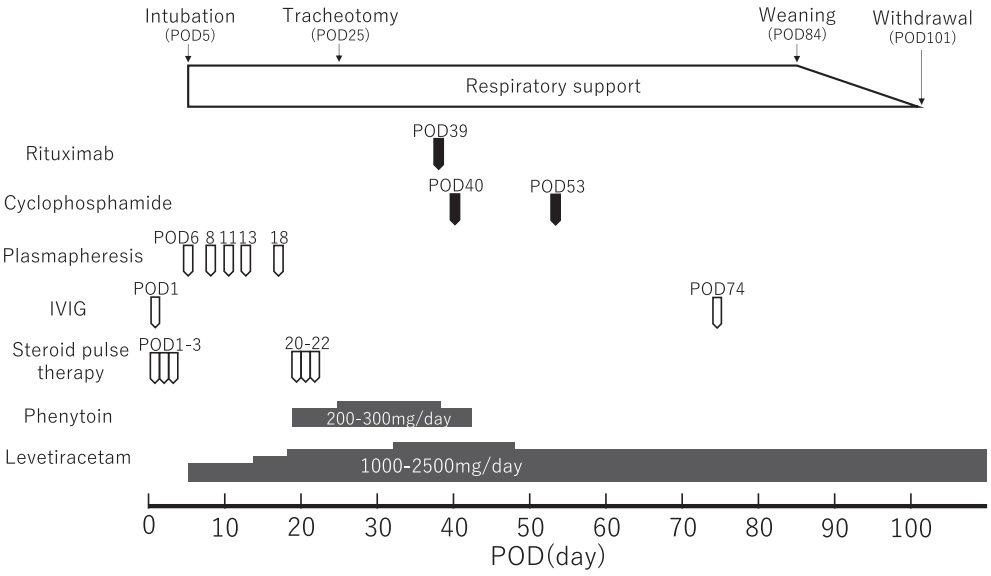

Fig. 2 Patient's postoperative course
Anticonvulsant drugs (levetiracetam, phenytoin) were administered. As first-line immunotherapy, steroid pulse therapy (1000 mg/d of methylprednisolone), intravenous immunoglobulin administration (25 g/d), and plasmapheresis were performed. Cyclophosphamide (1000 mg/d) and rituximab (500 mg/d) were administered as second-line immunotherapy. IVIG: intravenous immunoglobulin, POD: postoperative day.

was administered, and we extubated the patient after confirming adequate spontaneous respiration. She was thereafter transferred to the intensive care unit (ICU). At this point, she was able to maintain stable spontaneous respiration, and she had no seizures or psychiatric symptoms. The duration of surgery and anesthesia were 66 min and 143 min, respectively. The amount of blood loss was slight, and urine output was 550 mL. The volume of crystalloid infused intraoperatively was 680 mL.

Fig. 2 shows the patient's postoperative course. Immediately after her transfer to the ICU, she began first-line immunotherapy, high-dose immunoglobulin therapy (25 g/d of immunoglobulin G) and steroid pulse therapy (1000 mg/d of methylprednisolone). During the initial administration of the immunoglobulin G preparation, the patient complained of dyspnea, which was attributed to an allergic reaction to the immunoglobulin G preparation. Therefore, we discontinued high-dose immunoglobulin therapy but continued steroid pulse therapy for 3 d. Despite the surgery and immunotherapy, however, her symptoms related to anti-NMDAR encephalitis deteriorated. Due to apnea, fluctuating consciousness, seizures, and sustained involuntary movements, she was intubated and given respiratory support, with mechanical ventilation, under sedation with propofol was commenced on the 5th postoperative day (POD-5). The patient received levetiracetam (1000 mg/d) to control seizures. Plasmapheresis was performed to remove anti-NMDAR antibodies on POD-6, POD-8, POD-11, POD-13, and POD-18, but with no improvement in her symptoms. The test results issued on POD-14 indicated specific antibodies against NMDAR in the CSF specimen, confirming the anti-NMDAR encephalitis diagnosis. The final histopathological diagnosis of the right ovarian tumor was grade 2 immature teratoma. Phenytoin (200 mg/d) was added to levetiracetam for seizure control on POD-19. She subsequently underwent tracheotomy on POD-24, and was transferred to the general ward, although her symptoms of seizures, disturbance of consciousness, apnea, and involuntary movement persisted. As second-line immunotherapy, we administered rituximab (500 mg/d on POD-39 and POD-53) and cyclophosphamide (1000 mg/d on POD-40). Her consciousness level gradually improved by POD-61, and her seizures were well-controlled with 2000 mg/d of levetiracetam. Hence, we discontinued propofol on POD-67, and the patient began weaning from the respirator on POD-84. She was finally withdrawn from the respirator on POD-101 and discharged from our hospital in an ambulatory condition on POD-138.

Discussion

In 2005, Dalmau reported four cases of acute encephalitis with ovarian teratoma, characterized by memory deficits, psychiatric symptoms, consciousness disorders, and hypoventilation.[6] Specific autoantibodies to NMDAR were identified, and the syndrome was reported as paraneoplastic anti-NMDAR encephalitis associated with ovarian teratoma in 2007.[1] An observational cohort study, including 577 patients with anti-NMDAR encephalitis, reported that age at onset of the disease ranged from 8 months to 85 years, and 81% of the patients were female. The condition is more common in younger females.[7] Out of 577 patients, 220 patients (38%) had tumors, and 213 of the 220 patients (96.8%) were female.[7] Among the patients with anti-NMDAR encephalitis associated with tumors, 94% had an ovarian teratoma.[7] The long-term prognosis in these patients is generally good. However, 10%-20% of patients are resistant to treatment, and mortality is 4%-7%.[2, 7]

The clinical course of anti-NMDAR encephalitis has five phases: prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery phase.[8] In the prodromal phase, patients have symptoms suggestive of a common cold, such as fever and headache. In the psychotic phase, mood disorders (i.e., depression and anxiety) followed by schizophrenia-like symptoms (i.e., agitation, hallucinations, and delusions) and seizures are observed. These psychiatric symptoms usually manifest in fewer than two weeks after the prodromal symptoms. In the unresponsive phase, hypoventilation occurs due to respiratory center dysfunction, while the hyperkinetic phase is characterized by oral dyskinesia and finger athetosis, along with various symptoms suggestive of autonomic instability (i.e., tachycardia, bradycardia, excessive sweating, and/or salivation). In the gradual recovery phase, the consciousness level recovers slowly, and involuntary movements also improve. In patients with anti-NMDAR encephalitis, the detection of anti-NMDAR antibodies in the blood and/or CSF are essential for a definitive diagnosis.[2, 6]

According to the treatment strategy for anti-NMDAR encephalitis advocated by Dalmau in 2011,[2] early tumor resection and immunotherapy are recommended for patients with tumors and anti-NMDAR antibodies. The treatment duration can be shortened by early tumor resection.[1] Steroid pulse therapy, immunoglobulin therapy, and/or plasmapheresis are recommended as first-line immunotherapy for patients with and without tumors. Patients who do not respond to first-line immunotherapy can receive rituximab and/or cyclophosphamide as second-line immunotherapy. Long-term immunotherapy for one year is usually recommended because of the reported recurrence rate of 20%-25%.[2]

In the present case, we suspected anti-NMDAR encephalitis, so we performed an emergency laparoscopic salpingo-oophorectomy. We initiated first-line immunotherapy immediately following surgery without waiting for the antibody test results. The patient's symptoms did not respond to this therapy, and second-line immunotherapy was required. The treatment may have been refractory in this case because of a possible residual tumor. There are some cases in which anti-NMDAR encephalitis developed even from a tiny teratoma.[9, 10] However, in this case, the abdominal CT before surgery and laparoscopic inspection during surgery detected no abnormalities in the left ovary. Also, a follow-up CT two months after discharge confirmed no local recurrence and no tumor in the left ovary. Another possible reason for the resistance to first-line treatment was the lack of high-dose immunoglobulin therapy because of the patient's allergy. She underwent treatment for anti-NMDAR encephalitis for about four months with no recurrence of symptoms for over two years after her discharge.

There are several issues concerning the anesthetic management of patients with anti-NMDAR encephalitis. First, perioperative management is challenging because of various clinical features, such as psychiatric symptoms, seizures, and central hypoventilation. According to previous case reports,[4, 5, 11] some patients require preoperative respiratory support with mechanical ventilation and/or preoperative pharmacological therapy using a variety of drugs, such as steroids, anticonvulsants, and antipsychotics. Such situations might complicate anesthetic management. Second, the clinical course after surgery is different for each case.[1, 2, 6–8] In the present case, arousal from general anesthesia was uneventful. The patient maintained stable respiration spontaneously, and we did not observe any seizures or psychiatric symptoms related to anti-NMDAR encephalitis until POD-4. Subsequently, however, despite the postoperative immunotherapy, respiratory support was required due to apnea, a fluctuating level of consciousness, seizures, and sustained involuntary movements on POD-5. Thus, careful observation in the postoperative period is essential. Third, there are no established guidelines for the anesthetic management of patients with anti-NMDAR en-

cephalitis. Drugs interacting with NMDARs, i.e., NMDAR antagonists (ketamine, nitrous oxide, tramadol, and magnesium), should not be administered because of possible deterioration of symptoms. Therefore, benzodiazepines and opioids, which only minimally affect NMDARs, are preferred.[5, 12] There are some reports concerning the effects of volatile anesthetics and propofol on NMDARs. Hollman et al.[13] reported that isoflurane, sevoflurane, and desflurane inhibit the function of NMDARs in oocytes of the frog species, Xenopus, in a reversible, concentration-dependent, voltage-insensitive and noncompetitive manner, at a half-maximal inhibitory concentration of 1.2-1.3 minimum alveolar concentration, which is a clinically relevant concentration. Orser et al.[14] demonstrated that clinical concentrations of propofol reduce NMDA-evoked currents in murine hippocampal neurons by only 10%-20%. Thus, propofol has fewer inhibitory effects on NMDARs, so we chose propofol as the agent for induction and maintenance of general anesthesia in the present case. Also, we administered midazolam during the induction of general anesthesia due to its anticonvulsant effects.

Conclusion

We experienced the perioperative management of a patient with anti-NMDAR encephalitis associated with ovarian teratoma. The clinical course of anti-NMDAR encephalitis is varied. Thus, the perioperative management of these patients should be planned carefully in each case. Currently, there are no guidelines for the anesthetic management of patients with anti-NMDAR encephalitis. We suppose that the accumulation of case reports of this disease is important for the establishment of appropriate treatment and management guidelines.

Conflicts of interest: None declared.

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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