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CLINICAL STUDY PATIENT STUDIES

Clinical analysis of paraneoplastic encephalitis associated with ovarian teratoma

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Abstract
Background Recently, paraneoplastic encephalitis associated with ovarian teratoma has been described and related to an autoantibody. Methods: We describe four patients with ovarian teratoma-associated encephalitis (OTE) and compared their clinical pictures with those of 17 previously reported patients with OTE. Results: Clinically, OTE was characterized by the development of acute prominent psychiatric symptoms (20 of 21 patients), seizures (15 of 21 patients), and central hypoventilation (13 of 21 patients). Our patients had hypersalivation (three patients) and cardiac conduction problems (all patients); hypothermia was present in one patient. The mean time from the onset of OTE to tumor diagnosis was 19.6 ± 22.1 weeks. Ventilatory support was required for 54.9 ± 25.4 days on average. The white blood cell count in cerebrospinal fluid was 55.1 ± 61.2/mm^3. Twelve patients showed abnormalities on cranial MRI, involving areas such as the temporal regions (seven patients) or brainstem (four patients). In addition to tumor resection, 17 patients received some type of immunotherapy: 17 patients received corticosteroids, 10 received intravenous immunoglobulins, two received cyclophosphamide, seven received plasma exchange. Eighteen patients with OTE had neurological improvement, including 11 with full recovery. Conclusions: OTE presents with cardiac conduction problems and hypersalivation in addition to psychiatric symptoms, seizures, and central hypoventilation.

Keywords Encephalitis · Limbic encephalitis · Teratoma · Ovarian tumor · Paraneoplastic encephalitis

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Introduction

Paraneoplastic encephalitis is a rare neurological disorder associated with small cell lung carcinomas, lymphomas, thymomas, and testicular tumors. Recently, paraneoplastic encephalitis associated with ovarian teratoma has been described and related to an autoantibody that targets cell-membrane antigens [1–3]. Clinically, this condition is characterized by acute behavioral changes, prominent psychiatric symptoms, seizures, and central hypoventilation. The cerebrospinal fluid often shows evidence of inflammatory abnormalities, and neurological syndromes improve after tumor resection, immunotherapy, or both. We describe the clinical features of four patients with ovarian teratoma-associated encephalitis (OTE) and compare our findings with those of previously reported patients.

Case reports

Case 1

A 29-year-old woman who had fever and headache for 2 days presented with inappropriate behavior and impaired episodic memory of 1 days' duration. There was no known history of drug or alcohol use, and she had been in good health. She developed delusional thinking, with visual and auditory hallucinations. She would say, for example, ''I am

being watched by someone under the floor'' or that her ''parents' faces had changed''. On admission to our hospital in January 2002, she presented with a confusional state and pyrexia (37.4°C). The heart rate was 84 beats/min and regular, with a normal electrocardiogram (EKG). The blood pressure was 114/60 mm Hg. The results of general examinations were normal. Meningismus was absent. Blood cell counts and the results of routine biochemical analysis were normal. Twelve days later, the Glasgow coma score dropped from 11 to 7. Lumbar puncture showed 10 lymphocytes, a protein concentration of 35 mg/dl, and a glucose concentration of 72 mg/dl. Cranial T2-weighted MRI and FLAIR imaging showed no abnormalities. An EEG was mildly abnormal, with bilateral slow waves. Since partial seizures involving the right hand and secondary generalized seizures developed, anticonvulsant medications were started. Repeated lumbar puncture showed 43 lymphocytes, and the patient received intravenous acyclovir (250 mg three times daily) for a presumptive diagnosis of herpes simplex encephalitis. Arterial blood gas analysis indicated retention of carbon dioxide (59.4 mm Hg) on inhalation of a small amount of oxygen. Because there was no underlying respiratory disease, central hypoventilation was diagnosed. Perfusion MRI showed hyperperfusion in the whole brain, including the temporal regions and brainstem (Fig. 1), with normal T2 and FLAIR findings. She presented with involuntary chewing movements in the orolingual region. Twenty-four days after admission, respiratory failure developed. The patient was subsequently intubated and received mechanical ventilation. Since generalized seizures frequently occurred, sedation was started. The patient also received intravenous acyclovir (500 mg three times daily), dexamethasone (16 mg/day), and immunoglobulin (5 g/day). On the next day, hypothermia (34°C) of 4 hours' duration suddenly developed. Pelvic ultrasonography, performed in March, revealed a left ovarian mass measuring 10 cm in diameter. The serum levels of CA125 and AFP were normal. She had hypersalivation, with a saliva volume of up to 2 liters/day for

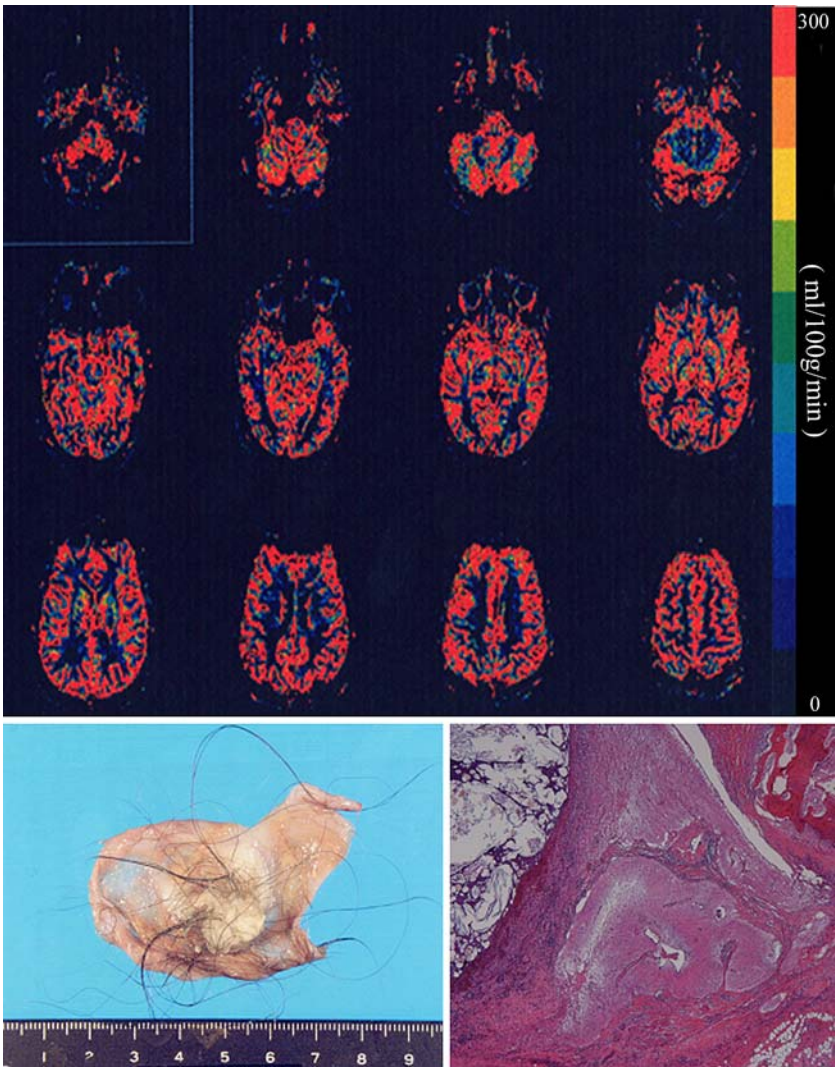

Fig. 1 Upper panel: Perfusion–weighted images were obtained with the use of a bolus of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA, 0.1 mmol/kg) at an injection rate of 2.0 ml/s. Twelve slices were obtained at 1 s intervals. The slice thickness was 5 mm, gap 5 mm, matrix 256 × 72, and field of view 300 mm. Images were obtained at 40 time points per slice. Perfusion MRI demonstrated marked hyperperfusion in the whole brain, predominantly in the cortical areas and involving the temporal regions and brainstem. Lower panel: the ovarian tumor contained many hairs (left panel). Materials employed in this study, i.e., 20% formalin-fixed and paraffin-embedded specimens, were retrieved from the surgical pathology files of the Pathology Section of Nara Medical University Hospital, Kashihara City, Nara, Japan. Histologic sections showed mature components of bone, hair, and neural structures (right panel).

1 month. On day 53 after admission, a cardiac arrhythmia, characterized by alternating repeated episodes of tachycardia (maximum heart rate, 170 beats/min) and bradycardia (minimum heart rate, 50 beats/min), was diagnosed. EKG monitoring showed frequent irregular R–R intervals. Serum levels of paraneoplastic autoantibodies (anti-Hu, anti-Yo, anti-RI, anti-Tr, anti-CV2, anti-Ma2, and amphiphysin antibodies) were normal. The voltage-gated potassium channel (VGKC) was 48 pmol/ℓ (normal control value $\leq$30 pmol/ℓ). PCR amplification of herpes simplex, varicella zoster, and cytomegalovirus DNAs was negative in CSF. The patient was given intravenous immunoglobulin infusions (5 g/day, 3 days). The cardiac arrhythmia resolved 2 weeks later. On day 68 after admission, ventilatory support was withdrawn. Repeated perfusion MRI demonstrated markedly decreased hyperperfusion. The level of consciousness increased, and the score on the Mini-Mental Status Examination (MMSE) was 13/30 in July and 23/30 in September. Pelvic ultrasonography demonstrated multiple ovarian masses, with diameters of 21 cm on the left side and 6 and 4 cm on the right side. In September, the bilateral ovarian tumors were removed via an ovarian cystectomy. The histopathological diagnosis was bilateral mature cystic teratoma (Fig. 1). The MMSE score in February 2003 was normal (30/30). Twenty-five months after admission, she was fully oriented, with no impairment of higher functions, including auditory comprehension, orientation, memory, cognition, and mentation. She was able to return to work and resume normal activities.

Case 2

In April 2005, a 32-year-old previously healthy woman had a frontal headache and fever for 9 days. Over the next few days, impaired memory, unusual behavior, and altered mental state developed. In May, the patient became apathetic, but could respond to questions. Findings on MRI scans and a laboratory workup were normal, expect for pleocytosis in CSF, with 116 white blood cells (99% lymphocytes). Since generalized seizures developed, the patient was transferred to our hospital. She was comatose, but responded to pain stimulation. Meningismus was present. The deep tendon reflexes were increased, with no pathological reflex. Brain MRI showed no abnormalities. The EEG was abnormal with diffuse slow waves and some epileptic discharges. VGKC were not detected. She received anticonvulsant medications, intravenous acyclovir, and immunoglobulin. One day after admission, she presented with hypersalivation and frequent seizures, leading to respiratory failure requiring ventilatory support. Twitching movements were present in the orolingual region. Sedating medication, immunoglobulin, methylprednisolone pulse therapy, and plasmapheresis were administered. On day 41 after hospitalization, tachycardia and bradycardia alternatively appeared. Temporary pacing was finally required because of sinus arrest for 5 seconds. On hospital day 61, temporary pacing was discontinued because the cardiac arrhythmia had disappeared spontaneously. In August, neurological disorders gradually improved. In September, hypersomnia and visual hallucinations appeared, but subsequently disappeared in October. In November, she was discharged. The score on the Wechsler Adult Intelligence Scale-Revised was 59. The Verbal and Performance IQ scores were 69 and 52, respectively. Pelvic ultrasonography demonstrated a 7.5×3.0 cm mass in the left ovary. She underwent a unilateral cystectomy. A mature teratoma of the ovary was diagnosed histopathologically in March 2006. At follow-up examination 17 months after admission, she had no impairment of higher functions, including auditory comprehension, orientation, memory, cognition, and mentation. She resumed working as a nurse.

Case 3

A 16-year-old girl with no clinically significant past medical history had a headache and fever for 2 weeks. In May 1995, she presented with visual hallucinations, unusual behavior, and delusional thinking. An EEG showed epileptic discharges in both temporal areas. Because the patient also had hypersomnia, she was admitted to our hospital. Anticonvulsant treatment was started. The results of general and neurological examinations were normal. On day 8 after admission, the level of consciousness decreased. Ataxic respiration and apnea appeared. Arterial blood gas analysis indicated retention of carbon dioxide (45.2 mm Hg). She had presented with twitching movements in the orolingeal region. Lumbar puncture showed 50 lymphocytes and a protein concentration of 21 mg/dl. Brain MRI showed no abnormalities. Since generalized seizures frequently occurred, sedation was started, in addition to acyclovir and intravenous methylprednisolone. Since hospital day 19, tachycardia with a maximal heart rate of 190 beats/min persisted, with decreased R–R intervals (CVRR; range 2.1–2.9%) on the EKG. Frequent seizures and hypersalivation developed. Intubation was required, and the patient became dependent on mechanical ventilatory support. After 3 weeks, neurological symptoms gradually improved. In September 1996, bilateral ovarian cystectomy was performed. Ovarian tumors, measuring 20 and 5 cm in diameter, were diagnosed to be mature cystic teratomas. At reexamination 27 months after admission, she had no impairment of higher functions, including auditory comprehension, orientation, memory, cognition, and mentation. She went back to school, with no problem.

Case 4

A 17-year-old girl who had been in good health had a headache for 2 weeks. In June 2006, she presented with unusual behavior and delusional thinking. On the next 2 days, partial seizures developed in the right hand, and she was admitted in a confusional state. Meningismus was absent. Myoclonic movements were present in the orolingual region and lower extremities. Lumbar puncture showed 81 white blood cells (99% lymphocytes) and a protein concentration of 35 mg/dl. PCR was negative for herpes simplex virus in the CSF. Brain MRI demonstrated no abnormalities. EEG was mildly abnormal, with diffuse slow discharges. VGKC and paraneoplastic autoantibodies (anti-Hu, anti-Yo, anti-RI, anti-Tr, anti-CV2, anti-Ma2, and amphiphysin antibodies) were not detected. The patient received intravenous acyclovir, dexamethasone, and immunoglobulin. On hospital day 9, frequent generalized seizures developed, requiring ventilatory support and sedation. In August, neurological symptoms improved, and ventilatory support was withdrawn. At about the same time, tachycardia (maximum heart rate, 180 beats/min) and bradycardia (minimum heart rate, 40 beats/min) with sinus arrest of uncertain cause alternatively appeared for about 1 month. In September, pelvic ultrasonography, CT, and MRI demonstrated an ovarian mass measuring 4 cm in a diameter with typical findings of teratoma. In October 2006, she undewent unilateral cystectomy and pathological diagnosis was mature teratoma. At follow-up 10 months after admission, the patient has emotional lability and mildly impaired memory, such as difficulty in recalling newly learned English words. However, she requires no assistance in activities of daily living and has resumed classes at school, without any problem.

Discussion

Our patients with OTE presented with acute behavioral changes and prominent psychiatric symptoms, seizures, and central hypoventilation, requiring admission to an intensive care unit and extended ventilatory support, similar to 17 previously described patients [1, 3–14]. These neurological disorders preceded the diagnosis of ovarian teratoma (Table 1).

Central hypoventilation has been reported in a few patients with paraneoplastic disorders involving the brainstem, hypothalamus, or both [15–17]. OTE is frequency associated with this complication (13 of 21 patients), requiring prolonged ventilatory support (range, 30–112 days). OTE is an extensive or multifocal type of encephalitis, and autopsy studies have shown nonspecific microglial activation throughout the gray and white matter of the brain, brainstem, and cerebellum, with scattered monocytes in perivascular spaces [9]. PET in OTE has shown scattered foci of hypermetabolism in the brain, not only in the temporal lobe, but also in the brainstem and cerebellum [1, 10], consistent with the findings in our patient (Case 1). Involvement of the brainstem may cause hypoventilation.

The onset of paraneoplastic limbic encephalitis is generally characterized by the development of behavioral disturbances, memory loss, and confusion. OTE initially shows prominent psychiatric symptoms (20 of 21 patients). On neuroimaging studies combining MRI, FDG-PET, and SPECT, eight patients had involvement of the temporal lobes, whereas five others showed no abnormalities. Mature teratoma of the mediastinum has also presented with psychiatric symptoms in two previously reported patients [10, 18], strongly suggesting an association between teratoma and psychiatric symptoms.

In OTE, including the patients in our series, seizures (12 generalized seizures, two partiel seizures, two myoclonic seizures) are generally followed by psychiatric symptoms. The mean time between seizures and the onset of psychiatric symptoms was 14.5 ± 22.0 days (range, 3–59 days) in the 6 patients for whom such information was available. Involuntary movements are often presented, such as chreoathetoid movements [3, 9] and oral dystonia, chewing movements, and myoclonic movements [3, 13, 14]. Our patients also showed involuntary movements for prolonged periods, especially in the orolingual region.

As compared with previously documented cases of OTE, our patients had hypersalivation, cardiac conduction disturbances (bradycardia-tachycardia syndrome in three and sinus arrest in two), and hypothermia. These complications appeared in our group of young women without a history of cardiac problems, suggesting a pathogenic mechanism similar to that responsible for the associated encephalitis. The development of these symptoms is most likely unrelated to the use of sedatives or antiepileptic drugs or to seizures. Previously, there were four patients with OTE in whom autonomic instability with wide variability in vital signs developed [3, 9, 14].

Paraneoplastic encephalitis is characterized pathologically by ‘‘patchy, multifocal’’ infiltrates in multiple areas of the nervous system [19]. Our patient (Case 1) also showed marked hyperperfusion, attributed to inflammation or seizures, in the whole brain, including the brainstem, on perfusion MRI. Involvement of the brainstem may affect the cardiac conduction system. Furthermore, cortico-limbic control of subcortical structures regulates autonomic function [20]. Disorders of the limbic system or thalamus can lead to dysautonomia. Involvement of these areas might also have contributed to the characteristic features of our patients.

Table 1 Clinical pictures of patients with ovarian teratoma-associated encephalitis

	reported patients(n = 17)	Case 1	Case 2	Case 3	Case 4
age[mean ± SD, yr]	25.7 ± 8.4	29	32	16	17
symptoms [%]					
psychiatric sydrome	94 (16/17)	+	+	+	+
central hypoventilation	59 (10/17)	+	+	+	±
seizures	65 (11/17)	+	+	+	+
decreased consciousness	41 (7/17)	+	+	+	+
involuntary movements	59 (10/17)	+	+	+	+
hypersomnia	24 (4/17)	–	+	+	–
cardiac arrythmias	18 (3/17)	+	+	±[e]	+
hypersalivation	0 (0/17)	+	+	+	–
hypothermia	12 (2/17)	+	–	–	–
ventilatory support [days]	59.6 ± 28.6 (5/17)	44	83	30	39
time from OTE to tumor diagnosis [weeks]	19.6 ± 22.1 (13/17)[a]	32	47	68	19
WBC in CSF [/mm^3]	55.1 ± 61.2 (14/17)[b]	10	25	50	81
abnormalities on neuroimaging [%]					
MRI	69 (11/16)	+[d]	–	–	–
SPECT	75 (3/4)	+[d]	+[d]	–	–
FDG-PET	100 (1/1)	NE	NE	NE	NE
treatment [%]					
surgery	82 (14/17)	+	+	+	+
corticosteroids	76 (13/17)	+	+	+	+
intravenous immunoglobulin	41 (7/17)	+	+	–	+
plasma exchange	35 (6/17)	–	+	–	–
cyclophosphamide	12 (2/17)	–	–	–	–
outcome [%]					
duration follow-up [months]	19.2 ± 13.9 (13/17)[c]	25	17	27	10
complete recovery [%]	47 (8/17)	+	+	+	–
residual memory deficit [%]	35 (6/17)	–	–	–	+

WBC–White blood cells, CSF–Cerebrospinal fluid, OTE–Ovarian teratoma-associated encephalitis, MRI-Magnetic resonance imaging
SPECT–Single-photon emission computed tomography, FDG–^{18}F-fluorodeoxyglucose, PET–Positron emission topography
NE–Not examined

[a] Other 2 patients presented with OTE 1 month after tumor disgnosis, [b]Other 3 patients showed no pleocytosis

[c] 13 patients with available information, [d]Hyperperfusion, [e]Persistent tachycardia

Cardiac conduction disorders in our patients spontaneously resolved after several types of immunotherapy, suggesting a possible association between circulating antibodies and the cardiac conduction system. Neurological syndromes associated with VGKC antibodies can be accompanied by limbic encephalitis, dysautonomia, particularly excessive sweating, and involvement of the cardiac conduction system [21, 22]. VGKC antibodies are key determinants of neuronal excitability in the brain and peripheral nervous system [23]. Morvan's syndrome with elevated VGKC antibodies has presented with frequent supraventricular extrasystoles accompanied by tachycardia [20]. Genetic defects of VGKC function can cause cardiac arrhythmias such as the slow Q-T syndrome [24]. Moreover, effects of VGKC antibodies on secretory tissue might explain the excessive salivation [21]. Although direct evidence is lacking, circulating antibodies in OTE might affect the cardiac conduction system or cause hypersalivation.

Recent studies have reported that OTE is associated with an autoantibody that targets novel cell-membrane antigens [1–3]. Such autoantibodies react with the hippocampus or tumors containing neuronal structures [3]. However, common paraneoplastic autoantibodies, such as anti-Hu or anti-Yo antibodies, were not detected in 16 of the 17 previously described patients with OTE, including ours; 1 patient with OTE had anti-Ri antibodies [6]. A low level of VGKC antibodies was detected in our patient (Case 1), but not in any of the 12 other patients with reported results for this antibody.

Mature teratoma was diagnosed on surgery and ovarian tumor resection in our patients. Among the 21 reported cases of OTE, including ours, teratoma was mature in 13, immature in seven, and mixed type in one. Neurological disorders preceded tumor diagnosis in 19 of the 21 patients. Neurological disorders improved in the four reported patients who underwent tumor resection alone. In addition to tumor resection, 17 patients received some type of immunotherapy: 17 patients received corticosteroids, 10 received intravenous immunoglobulins, two received cyclophosphamide, and seven received plasma exchange. One of these patients, who received corticosteroids without surgical intervention, showed full recovery [10]. Our patient appeared to show some improvement in neurological disorders before tumor resection, suggesting that immunotherapy may be therapeutically useful. However, two patients, one of whom did not undergo tumor resection while the other received corticosteroids alone, died of neurologic disease progression [3]. The relative contribution of these treatments to neurological improvement was difficult to ascertain in our study; further studies are therefore awaited. Eighteen patients with OTE had neurological improvement, including 11 with full recovery. In 10 patients with available information, the mean time between the development of the main neurological syndrome and initial evidence of improvement was 10.4 ± 4.1 weeks (range, 4–16 weeks).

Clinicians should be aware that OTE may present with cardiac conduction problems and hypersalivation in addition to psychiatric symptoms, seizures, and central hypoventilation. These signs and symptoms have to be managed effectively during the course of OTE.

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