PARANEOPLASTIC ENCEPHALITIS ASSOCIATED WITH OVARIAN TERATOMA: CLINICAL PICTURES AND N-METHYL-D-ASPARTATE RECEPTOR ANTIBODIES

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Abstract : Background: Recently, a new category of paraneoplastic encephalitis associated with ovarian teratoma has been described and associates with antibodies to NR1/NR2 heteromers of the N-methyl-D-aspartate receptor (NMDAR).

Methods: We describe clinical pictures of 26 patients with ovarian teratoma-associated encephalitis (OTE) and the presence of NMDAR antibodies.

Results: Clinically, OTE was characterized by the development of acute prominent psychiatric symptoms (25 of 26 patients), seizures (19 of 26 patients), central hypoventilation (18 of 26 patients) and involuntary movements (19 of 26 patients). Ventilatory support was required for 84.5 ± 71.8 days on average. The white blood cell count in cerebrospinal fluid was 50.0 ± 56.6/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, twenty patients received some type of immunotherapy. Twenty-three patients with OTE had neurological improvement, including 14 with full recovery. Immunocytochemical studies showed that cells expressing NR1/NR2 heteromers reacted strongly with the CSF of patients with OTE.

Conclusions: Neurologists must be aware of the syndrome described above and evaluate antibodies to NR1/NR2B heteromers of the NMDAR. Detection of these antibodies should prompt the search for an ovarian teratoma and the administration of immunotherapy.

Key words : paraneoplastic encephalitis, ovarian teratoma, NMDAR

INTRODUCTION

Paraneoplastic encephalitis is a rare neurological disorder associated with small cell lung carcinomas, lymphomas, thymomas, and testicular tumors. Recently, a new category of paraneoplastic encephalitis associated with ovarian teratoma (OTE) has been described and related to an autoantibody that targets cell-membrane antigens[1-4]. This disorder results in prominent psychiatric symptoms, seizures, autonomic dysfunction, dyskinesias and hypoventilation, and associates with antibodies to NR1/NR2 heteromers of the N-methyl-D-aspartate receptor (NMDAR)[1,2,5-8]. This disorder is referred to as "anti-NMDA receptor encephalitis"[1]. The current review focuses on 26 patients with OTE[1-19] and this immune-mediated encephalitis.

Characteristic Neurological Findings

Behavioral changes and prominent psychiatric symptoms

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 such as shizophrenia-like symptoms, delusion, confusion, or hallucinations (25 of 26 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,[15, 20] strongly suggesting an association between teratoma and psychiatric symptoms.

Central hypoventilation

Central hypoventilation has been reported in a few patients with paraneoplastic disorders involving the brainstem, hypothalamus, or both[21-23]. OTE is frequently associated with this complication (18 of 26 patients), requiring prolonged ventilatory support (range, 30-270 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[14]. 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[3,15], consistent with the findings of perfusion MRI in our patient (see [5] for details). Involvement of the brainstem may cause hypoventilation.

Seizures

In OTE, seizures (16 generalized seizures, two partial 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

Long-lasting involuntary movements (IVMs) (maximum duration, 12 months) often occur (19 of 26 patients). Such IVMs include dyskinesias[7], chreoathetoid movements[1,14], oral dystonia, chewing movements, and myoclonic movements[1,18,19], especially in the orolingual region. Extensive monitoring with EEG showed the absence of paroxysmal discharges, suggesting that the movements were not epileptic[7]. These IVMs are usually refractory to antiepileptic medication and sedatives[1,5,7]. Refractory IVMs are a major clinical problem. Their underlying mechanism remains unclear. The N-acetylaspartate (NAA)/creatine (Cr) ratio on MR spectroscopy of the basal ganglia and thalamus were reduced during the course of the IVMs, suggesting that these IVMs were extrapyramidal in origin (Kataoka et al, unpublished data).

Autonomic instability

Previously, there were nine patients with OTE in whom autonomic instability with wide variability in vital signs developed[1,2,5,14,19]. OTE had hypersalivation, cardiac conduction disturbances (bradycardia-tachycardia syndrome or sinus arrest), and hypothermia[2,5]. The development of these symptoms is most likely unrelated to the use of sedatives or antiepileptic drugs or to seizures. These complications appeared in group of young women without a his-

tory of cardiac problems, suggesting a pathogenic mechanism similar to that responsible for the associated encephalitis. Although direct evidence is lacking, circulating antibodies in OTE or brainstem involvement might disturb autonomic stability or the cardiac conduction system[5]. These signs and symptoms have to be managed effectively during the course of OTE[5].

ANCILLARY TESTS

Neuroimaging

Many patients with OTE do not have abnormalities on cranial MRI or when abnormali-

Table 1. Clinical pictures of patients with ovarian teratoma-associated encephalitis, including our patients (Cases 1 to 4)

	reported patients(n=22)	Case 1	Case 2	Case 3	Case 4
age [mean±SD, yr]	25.4±8.0	29	32	16	17
symptoms [%]					
psychiatric sydrome	95 (21/22)	+	+	+	+
central hypoventilation	64 (14/22)	+	+	+	±
seizures	68 (15/22)	+	+	+	+
decreased consciousness	41 (7/17)	+	+	+	+
involuntary movements	68 (15/22)	+	+	+	+
hypersomnia	24 (4/17)	-	+	+	-
cardiac arrythmias	18 (3/17)	+	+	±※※	+
hypersalivation	6 (1/18)	+	+	+	-
hypothermia	12 (2/17)	+	-	-	-
ventilatory support [days]	102.3±82.4 (8/22)	44	83	30	39
time from OTE to tumor diagnosis [weeks]	19.6±22.1 (13/22)*	32	47	68	19
WBC in CSF [/mm^3]	51.8±61.4 (18/22)**	10	25	50	81
abnormalities on neuroimaging [%]					
MRI	57 (12/21)	+'※	-	-	-
SPECT	80 (4/5)	+'※	+'※	-	-
FDG-PET	100 (1/1)	NE	NE	NE	NE
treatment [%]					
surgery	68 (15/22)	+	+	+	+
corticosteroids	73 (16/22)	+	+	+	+
intravenous immunoglobulin	36 (8/22)	+	+	-	+
plasma exchange	27 (6/22)	-	+	-	-
cyclophosphamide	9 (2/22)	-	-	-	-
outcome [%]					
duration follow-up [months]	19.2±13.9 (13/22)***	25	17	27	10
complete recovery [%]	50 (11/22)	+	+	+	-
residual memory deficit [%]	36 (8/22)	-	-	-	+

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, *other 2 patients presented with OTE 1 month after tumor disgnosis, ** other 3 patients showed no pleocytosis

***13 patients with available information, ※hyperperfusion, ※※persistent tachycardia

ties occur they usually involve medial temporal lobes, insular region and less frequently cerebral cortex[1,7]. PET in OTE has shown scattered foci of hypermetabolism in the temporal lobe, brainstem and cerebellum[3,15]. Although no abnormal findings were detected on conventional MRI, the perfusion MRI showed hyperperfusion in the whole brain (see[5] for details).

CSF Findings

CSF lymphocytic pleocytosis was identified in all of our reported patients with OTE (see Table 1), consistent with previous findings (9–219 cells/$\mu\ell$; median 24 cells/$\mu\ell$)[1]. All patients with OTE underwent a battery of serum and CSF diagnostic tests. The results were negative or normal for viral, bacterial, and fungal infections; collagen–vascular autoimmune disorders; thyroid autoimmunity; and comprehensive panels of paraneoplastic and voltage–gated potassium channel (VGKC) antibodies.

Associated Tumors

Among the 25 reported cases of OTE, teratoma was mature in 16, immature in eight, and mixed type in one. Neurological disorders preceded tumor diagnosis in 24 of the 26 patients.

Treatment and Outcome

Neurological disorders improved in the 4 reported patients who underwent tumor resection alone. In addition to tumor resection, 20 patients received some type of immunotherapy: 20 patients received corticosteroids, 11 received intravenous immunoglobulins, two received cyclophosphamide, and seven received plasma exchange. One of these patients, who received corticosteroids without surgical intervention, showed full recovery[15]. Two patients, one of whom did not undergo tumor resection while the other received corticosteroids alone, died of neurologic disease progression[1]. Twenty–three patients with OTE had neurological improvement, including 14 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).

Case history of our patient with OTE

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, she presented with a confusional state and pyrexia (37.4 ℃). The heart rate was 84 beats/min and regular, with a normal electrocardiogram (EKG). The blood pressure was 114/60 mmHg. The results of general examinations were normal. Meningismus was absent. Blood cell counts and the results of routine biochemical analysis were normal. Twelve days after admission, 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 sec-

ondary 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 mmHg) on inhalation of a small amount of oxygen. Because there was no underlying respiratory disease, central hypoventilation was diagnosed. 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 ℃) of 4 hours' duration suddenly developed. Pelvic ultrasonography 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 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-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. The level of consciousness increased, and the score on the Mini-Mental Status Examination (MMSE) was 23/30. Pelvic ultrasonography demonstrated multiple ovarian masses, with diameters of 21 cm on the left side and 6 and 4 cm on the right side. Nine months after admission, the bilateral ovarian tumors were removed via an ovarian cystectomy. The histopathological diagnosis was bilateral mature cystic teratoma. One year after admission, the MMSE score 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.

Determination of antibodies to NMDA receptor

Immunocytochemical studies were performed as previously described[1]. In brief, HEK 293 cells were transfected with NR1 and NR2 plasmids to express NR1/NR2 heteromers. We investigated the presence of these antibodies in archived frozen CSF of three of the our reported patients with OTE (see[5] for details, patient 1, 3 and 4. Similar to previous findings[1], cells expressing these heteromers, but not non-transfected cells, reacted strongly with the CSF of patients 1 and 4, obtained at early stages of the disease (Fig. 1, A and B), and reacted weakly with the CSF of patient 3, obtained at a later stage of the disease (Fig. 1 C)[6]. From patients 3 and 4, samples of CSF were available for follow-up of antibody titers. In both patients, the follow-up CSF samples were obtained while recovering from the neurological

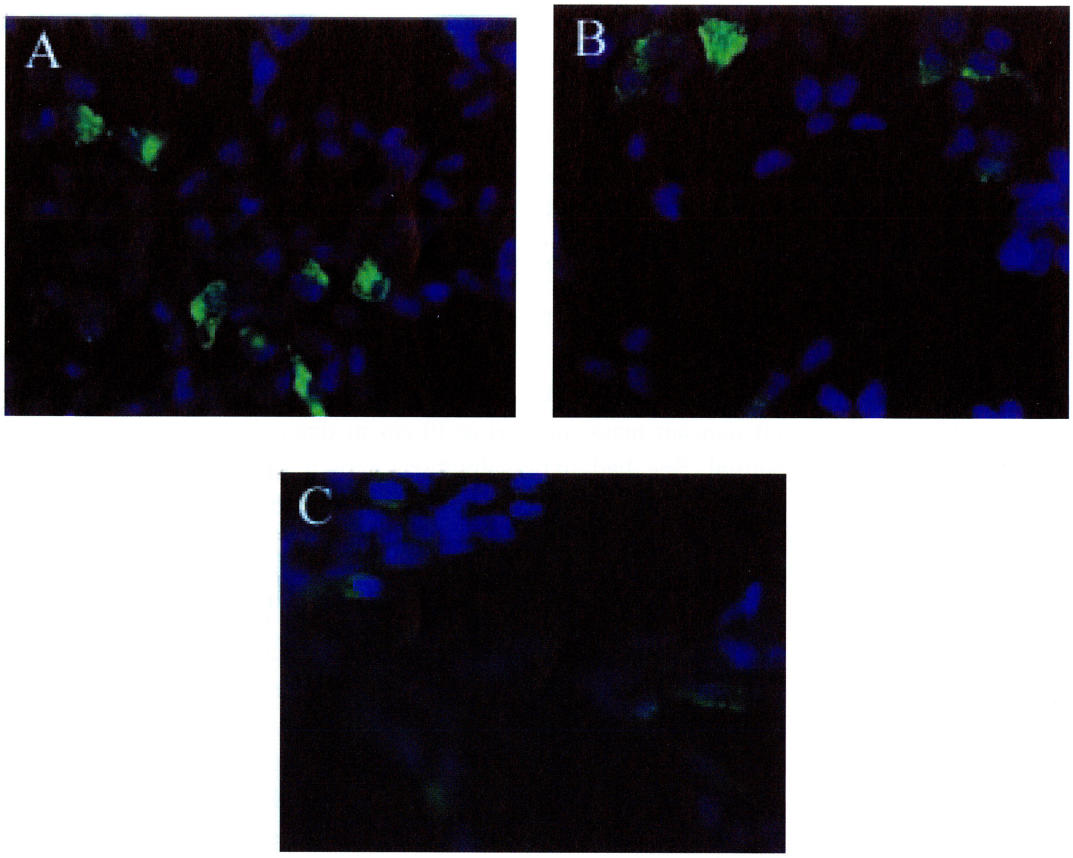

Fig. 1. Reactivity of patients' CSF antibodies with NR1/NR2 heteromers of the NMDAR.
HEK 293 Cells expressing NR1/NR2B heteromers show intense reactivity with the CSF (diluted 1:10) of patients 1 (panel A) and 4 (panel B) and weaker reactivity with CSF of patient 3 (panel C). Non-transfected cells (visible with nuclear staining by DAPI) show no reactivity.

deficit. When compared with the antibody titers at symptom presentation, the follow-up CSF samples of both patients showed a substantial decrease of antibody titers[6]. In patient 3 the antibodies were no longer detectable in her CSF and in patient 4 the antibody titers (obtained by serial dilutions of paired samples) were 1:160 at symptom presentation and 1:20 while recovering.

Patients' tumors contained nervous tissue expressing NMDA receptor

Tumors showed mature- and immature-appearing neurons together with networks of fibers with a variable density that expressed MAP2 (a marker of neurons and dendritic processes) [1]. The atypical nervous tissue strongly expressed NR2 subunits of NMDAR; colocalization of reactivities was observed when tumors were incubated with commercially available antibodies to NR2B or NR2A and patients' antibodies[1].

CONCLUSION

Neurologists must be aware of the syndrome described above and evaluate antibodies to NR1/NR2B heteromers of the NMDAR. Detection of these antibodies should prompt the search for an ovarian teratoma and the administration of immunotherapy.

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