Rinsho Shinkeigaku (Clin Neurol) 2024;64:564-571
doi: 10.5692/clinicalneurol.cn-001943

Case Report

Cancer-associated neuromyelitis optica spectrum disorder: a case report with literature review

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Abstract: Neuromyelitis optica spectrum disorders (NMOSD) is one of autoimmune inflammatory diseases and is characterized by area postrema syndrome, brainstem syndrome, optic neuritis, and/or myelitis. Typical myelitis is longitudinally extended transverse myelitis (LETM) which extends over three vertebral bodies. Several previous case reports have suggested association between cancer and NMOSD. A 50-year-old woman had breast cancer and underwent mastectomy and, 10 months later, she had developed acutely progressive dysbasia. Spine MRI showed LETM in 13 vertebrae length and blood test revealed positive anti-aquaporin 4 (anti-AQP4) antibody based on enzyme-linked immunosorbent assay with index of over 40. She was treated by intravenous methylprednisolone, plasma exchange, and intravenous immunoglobulin, followed by oral prednisolone. The condition had mostly recovered after the treatment. A small population of NMOSD has the aspect of paraneoplastic neurological syndrome. The age of onset in patients with cancer-associated NMOSD tends to be higher than that in individuals with NMOSD due to any causes of NMOSD.

Key words: anti-AQP4 antibody, LETM, NMOSD, paraneoplastic neurological syndrome

Abbreviations: anti-AQP4, anti-Aquaporin-4; APS, area postrema syndrome; BS, brainstem syndrome; CSF, cerebrospinal fluid; CT, Computed Tomography; EDSS, Expanded Disability Status Scale of Kurtzke; ELISA, enzyme-linked immunosorbent assay; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LETM, longitudinally extended transverse myelitis; MRC, Medical Research Council; MRI, Magnetic Resonance Imaging; NMOSD, Neuromyelitis Optica Spectrum Disorders; ON, optic neuritis; PE, plasma exchange; PLS, prednisolone

Background

Neuromyelitis optica spectrum disorders (NMOSD), one of autoimmune inflammatory diseases, is characterized by area postrema syndrome, brainstem syndrome, optic neuritis, and/or myelitis. Some cases of NMOSD are associated with cancer, and our case might have a paraneoplastic neurological syndrome. Typical myelitis is longitudinally extended transverse myelitis (LETM) which extends over three vertebral bodies. Here we report a case of NMOSD, LETM with 13 vertebrae length, which was developed after breast cancer. We also conducted literature review regarding relationships of cancer, anti-aquaporin 4 antibody, and LETM.

Case presentation

A 51-year-old woman underwent surgery for breast cancer of p-T2N2M0 stage IIIA. After the surgery, she underwent chemotherapy (four courses of intensive dose epirubicin plus cyclophosphamide and four courses of intensive dose paclitaxel) and radiation therapy (50 Gy/25 Fr). She also received daily oral tamoxifen after surgery. In this period, she was able to work 8 hours per day without recurrence of breast cancer. Ten months after the surgery, she developed acutely progressive dysbasia. Six days after the onset of dysbasia, she visited her breast surgeon in our hospital and was referred to a neurologist. She had no other symptoms and no episodes of recent infectious

(Received November 10, 2023; Accepted March 24, 2024; Published online in J-STAGE on July 27, 2024)
This article is available in Japanese with an abstract in English at www.jstage.jst.go.jp/browse/clinicalneurol.

diseases or vaccinations during the period after the breast surgery until consultation to the neurologist. She had no other significant past medical history. She had no family history of neurological diseases.

On physical examination, blood pressure was 133/82 mmHg, pulse 60/minute, respiratory rate 16/minute, temperature 36.4 degree Celsius, and pulse oximetry oxygen saturation 98% in room air. The height was 150 cm, and the weight was 42 kg. There was dysbasia. Neurological exam by the neurologist revealed muscle weakness and Medical Research Council (MRC) score was 2 over 5 in flexion of elbow joint, flexion of hip joint, flexion of knee joint, and left ancle dorsiflexion. MRC score of right ancle dorsiflexion was 3 over 5 (MRC score 31/60). Deep tendon reflexes were exaggerated in left upper limb and reduced in lower limb with dominance in right lower limb. Sensation of pain and tactile were lost in the region below Th7 level. Sense of vibration was reduced in right upper limb and lost in both lower limbs. Positional sense was normal in upper limbs, decreased in right lower limb, and lost in left lower limb. She had bladder and bowel dysfunction. A diagnosis of myelitis was considered, and she was hospitalized on the same day.

Blood tests showed increased erythrocyte sedimentation rate (21 mm/hour) and mild elevation of alanine aminotransferase, creatine kinase, and C-reactive protein (Table 1). Serum albumin, creatinine, and sodium were slightly lower than ranges of normal limits. HbA1c was 6.3%. Blood coagulation test results were all normal. The relatively low serum free T3 of 1.80 pg/m/ was considered as low T3 syndrome secondary to the primary neurological disease. In cerebrospinal fluid (CSF) test on hospital day 1, white blood cell count was 42/mm^3 (reference range, 0–3/mm^3), and protein was 94 mg/d/. Bacterial culture of CSF did not grow organisms and CSF cytology was negative for malignant cells. She underwent MRI, showing myelitis with increased signal intensity lesion in the spine of C4 to Th9 levels (Fig. 1A, B). Regarding the Functional systems (FS) scores at the time of hospital admission, she used wheelchair with riding support because she had paraplegia in lower limbs (FS 3 in pyramidal function), cerebellar function was normal (FS 0 in cerebellar function), lost all sensations in both lower limbs (FS 5 in sensory), normal in brainstem function (FS 0 in brainstem function), lost the function of bladder and rectum (FS 6 in sphincter function), no disorder in visual function (FS 0 in visual function), normal mental or cerebral function (FS 0 in mental function), and no other neurologic findings attributed to NMOSD (FS 0 in other function). Her Expanded Disability Status Scale of Kurtzke (EDSS) at the time of hospital admission was 7.5.

NMOSD or spinal venous infarction were considered as most likely diagnosis, although the 13 vertebrate length lesion is not common in both. Since tamoxifen has side effect of thrombosis and she had menopause by chemotherapy, from day 1 we changed tamoxifen to anastrozole. Venous infarction of spinal cord was also considered as one of the differential diagnosis lists, but contrast-enhanced computed tomography (CT) and MRI showed no evidence of infarction of spinal cord (Fig. 1C, D).

From day 1 to day 20 she was treated by intravenous concentrated glycerin fluid. From day 2 to day 4, she received a half of pulse dose intravenous methylprednisolone (IVMP), 500 mg/day. During the half dose IVMP use, on day 3, MRC score of left lower limb was reduced to 0/5, and it was switched to the full dose IVMP, 1,000 mg/day during day 6 to 8 and it was repeated during day 13 to 15. During the period of IVMP use, her symptoms did not improve. On day 20, serum anti-aquaporin 4 (anti-AQP4) antibody test turned around to be positive based on enzyme-linked immunosorbent assay with index of over 40, and diagnosis of NMOSD was made, and thus plasma exchange (PE) was started on day 21. After the first PE, MRC score of left lower limb improved from 0 to 1. PE was repeated on day 23, 25, 28, and 30. MRC score of left lower limb was improved to 3/5 on day 30. From day 31 to 35, intravenous immunoglobulin (IVIg) was administered at 400 mg/day. However, IVIg use did not improve the muscle weakness. Thus, additional PE was conducted on day 39 and 42, but these additional PE did not improve the muscle weakness. After the treatment for acute period, from day 43 oral prednisolone (PLS) was started at the dose of 20 mg/day as the maintenance therapy. During the hospitalization, serum tumor markers were negative and contract-enhanced CT did not show findings of tumor recurrence or metastasis.

On day 69 she was transferred to a specialized rehabilitation hospital. At that time, her EDSS was 6.5, and she had paraplegia in lower limbs (FS 3) and lost the function of bladder and rectum (FS 6), although all sensory impairment in both lower limbs had recovered (FS 2). After rehabilitation, her muscle weakness improved, and she was discharged from the rehabilitation hospital. She could walk alone without an aid. When she visited our neurology clinic on day 239, MRC score was 5/5 in all muscles. Her EDSS was 0. However, she still had defecation disorder and also had pain in right upper limb. As her symptoms improved, dose of PLS was reduced to 10 mg/day. Anti-AQP4 antibody turned around to be negative on day 239. MRI was performed on day 252, showing high signal intensity from C6 to Th9 level in the spine (Fig. 2). Length of the lesion was remarkably improved compared to the finding of MRI on day 1.

Throughout this period, she took anastrozole daily, and our breast surgeon had diagnosed she has no recurrence of breast cancer.

Discussion and conclusions

This case illustrates that NMOSD could be associated with a preceding breast cancer, although the cancer was surgically resected and was also treated by chemotherapy. Our case has relatively long LETM lesion, which may characterize a paraneoplastic syndrome. We conducted a literature search of

Table 1 [Blood and CSF test results on day 1] The anti-AQP4 antibody is positive.

<Blood cell count>			<Biochemistry>			<Antibody>			<Infection>			<CSF>		
WBC	6,900	/μl	Alb	3.1	g/dl	Anti-DNA	≤1.7		RPR	0.4	R.U.	Cell	42	/3
Hb	12.1	g/dl	AST	24	U/l	Anti-nuclear	<40		HBs antigen	0.00	IU/ml	M:P	15:27	N:L
MCV	88.1	fl	ALT	36	U/l	PR3-ANCA	<1.0		HCV antibody	0.05	S/CO	Protein	94	mg/dl
Plt	31.2	$\times 10^4/\mu l$	γ-GTP	31	U/l	MPO-ANCA	<1.0		HIV antibody	0.22	S/CO	Glucose	42	mg/dl
ESR	21	mm	BUN	9.5	mg/dl	Anti-AChR	≤0.3		IGRA	Negative		CK	4	U/l
<Coagulation>			Cre	0.40	mg/dl	Ati-AQP4	≥40	(ELISA)	<Vitamin>			OCB	(-)	
PT-INR	1.09		CK	247	U/l	<tumor marker>			Vit. B_1	38.1	μg/dl			
APTT	26.0	Second	Na	130	mEq/l	CEA	1.1	ng/ml	Vit. B_6	3.4	ng/ml			
Fib	314	mg/dl	K	4.0	mEq/l	CA15-3	7.5	U/ml	Vit. B_{12}	379	pg/ml			
D-dimer	0.3	ng/ml	IgG	896	mg/dl	<Endocrine>			folic acid	8.0	ng/ml			
PC activity	125		CRP	0.2	mg/dl	TSH	1.80	μIU/l	<Other>					
PS activity	94		<Blood glucose>			fT4	1.01	ng/dl	sIL2-R	463	U/ml			
PT-INR	1.09		Blood sugar	103	mg/dl	fT3	1.80	pg/dl						
			HbA1c	6.3	%									

CSF: cerebrospinal fluid, WBC: White Blood Cell, Hb: Hemoglobin, MCV: Mean Corpuscular Volume, Plt: Platelet, ESR: Erythrocyte Sedimentation Rate, PT-INR: Prothrombin Time - International Normalized Ratio, APTT: Activated Partial Thromboplastin Time, Fib: Fibrinogen, D-dimer: Dimerized Plasmin Fragment D, PC: Protein C, PS: Protein S, Alb: Albumin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, γ-GTP: Gamma-Glutamyl Transpeptidase, BUN: Blood Urea Nitrogen, Cre: Creatinine, CK: Creatine Kinase, Na: Sodium, K: Potassium, IgG: Immunoglobulin G, CRP: C-Reactive Protein, HbA1c: Hemoglobin A1c, DNA: Anti-Deoxyribonucleic Acid, ANA: Anti-Nuclear Antibody, PR3-ANCA: Proteinase 3 Anti-Neutrophil Cytoplasmic Antibody, MPO-ANCA: Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody, AChR: Anti-Acetylcholine Receptor, AQP4: Anti-Aquaporin-4, ELISA: enzyme-linked immunosorbent assay, CEA: Carcinoembryonic Antigen, CA15-3: Cancer Antigen 15-3, TSH: Thyroid Stimulating Hormone, fT4: Free Thyroxine, fT3: Free Triiodothyronine, RPR: Rapid Plasma Reagin, HBs: Hepatitis B Surface, HCV: Hepatitis C Virus, HIV: Human Immunodeficiency Virus, IGRA: Interferon Gamma Release Assay, Vit: Vitamin, sIL2-R: soluble Interleukin-2 Receptor, M:P: mononuclear cell to polynuclear cell ratio, OCB: oligoclonal band

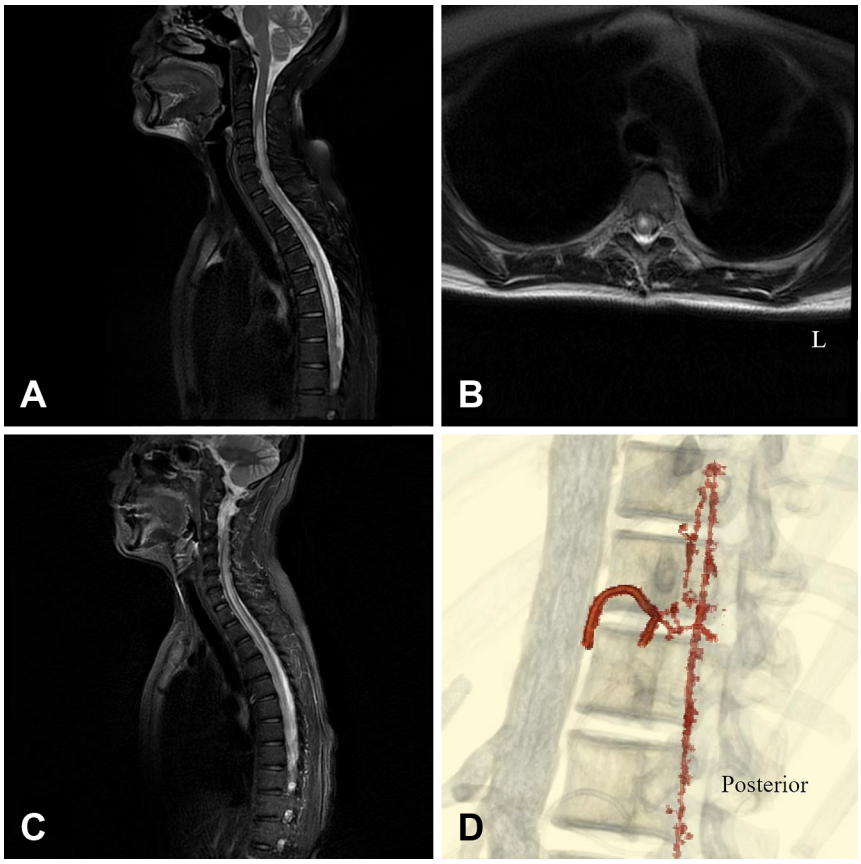

Fig. 1 T_2 weighted MRI images.
A) MRI sagittal T_2 weighted image on day 1 which show LETM in C4 to Th9 levels. B) MRI axial T_2 weighted image on day 1 in Th3 level. C) CE-MRI sagittal T_1 weighted image on day4. D) CTA on day 5 in spinal artery. Abbreviations: CTA; computerized tomographic angiography, CE-MRI; contrast-enhanced magnetic resonance imaging, LETM; longitudinally extended transverse myelitis.

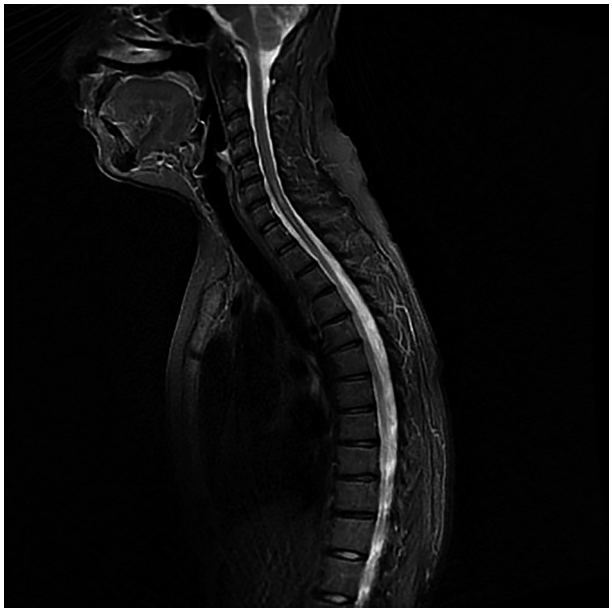

Fig. 2 T_2 weighted MRI after treatment.
MRI sagittal T_2 weighted image on day 252.

reports of NMOSD associated with cancer by Google Scholer (R) (search words: "NMOSD" "cancer" "LETM"), and we identified 22 case reports which included the description of sex, age, type of cancer, primary organ of cancer, treatment for NMOSD, interval between the onset of cancer and NMOSD, length of LETM, and outcome. Anti-AQP4 antibodies are positive in all cases in the previous literature and in this case. We summarized the clinical characteristics by adding our case to these case reports (Table 2)[1)–22)].

Also, we examined female proportions, age of onset, death rate, length of LETM and showed no significant difference between cases with any causes of NMOSD[23)] and cancer-associated NMOSD with LETM (Table 3). Because of the literature review regarding only cases with various background, we could not compare length of LETM by head-to-head. However, there might be trend that length of LETM in cases of cancer associated NMOSD is longer than cases with any causes of NMOSD.

Our patient made a remarkable recovery after treatment. Regarding factors related to outcome, candidate factors included age of onset, sex, type of cancer, diagnostic interval between

Table 2 [Profile of LETM patients in cancer-associated NMOSD with LETM[1)–22)]] All cases were treated by IVMP.

	about cancer				symptoms										treatment							
reference	age	sex	organ of tumor	pathological type	diagnostic interval between onset of cancer and NMOSD (month)	length of LETM (veartebrae bodyis)	anti- AQP4 Ab in seram	AQP4 staining in tumor	motor symptoms in the onset	sensory symptoms in the onset	visual symptoms in the onset	reflex distureba nce in the onset	nausea, vomiting in onset	bladder and rectal disturbance in onset	other symptom s in the onset	IVMP	IVIg	PE	rituximab	azathioprine	PLS	other tretment	outcome
1	15	F	ovary	teratoma	4	5	p	p	+	n.l.	n.l.	n.l.	+	n.l.	+	+	n/a	n/a	+	n/a	n/a	+	improved
2	28	F	blood	hematological malignancy	12	6	p	n.l.	n.l.	n.l.	+	n.l.	+	n.l.	n.l.	+	n/a	n/a	n/a	n/a	n/a	n/a	improved
3	31	F	kidney	carcinoma	0	11	p	p	+	–	+	–	n.l.	n.l.	+	+	+	n/a	n/a	n/a	+	tacrolimus	improved
4	32	F	brest	carcinoma	–2	6	+	n.l.	+	n.l.	n.l.	n.l.	n.l.	n.l.	+	+	n/a	n/a	n/a	n/a	n/a	chemotherapy (include rituximab)	improved
5	34	F	brain	carcinoma	–2	4	p	n/a	n.l.	+	+	n.l.	n.l.	n.l.	n.l.	+	n/a	n/a	n/a	n/a	n/a	n/a	improved
6	37	F	lung	carcinoma	1	13	p	p	+	n.l.	+	–	–	–	–	+	n/a	n/a	n/a	n/a	+	n/a	not improved
1	41	F	ovary	teratoma	–3	13	p	p	+	+	n.l.	n.l.	+	n.l.	+	+	n/a	n/a	n/a	n/a	+	mycophenolate mofetil	improved
7	42	F	ovary	teratoma	0	20	p	p	+	+	n.l.	+	+	+	n.l.	+	+	+	+	n/a	n/a	n/a	improved
8	43	F	brest	carcinoma	–10	12	p	n	n.l.	n.l.	+	n.l.	n.l.	n.l.	+	+	n/a	n/a	+	n/a	n/a	n/a	improved
9	50	F	ovary	teratoma	–10	3	p	n/a	+	+	n.l.	n.l.	n.l.	n.l.	+	+	n/a	+	n/a	n/a	n/a	n/a	improved
our case	51	F	brest	carcinoma	10	13	n	n/a	+	+	–	+	–	+	–	+	+	+	n/a	n/a	n/a	n/a	improved
10	54	F	ovary	carcinoma	–3	5	n	n/a	+	n.l.	n.l.	n.l.	+	n.l.	+	+	n/a	+	n/a	+	+	mitoxanthrone	improved
8	58	F	blood	hematological malignancy	5	9	p	n.l.	+	+	n.l.	n.l.	n.l.	+	–	+	n/a	n/a	n/a	+	n/a	n/a	improved
11	59	M	renal	carcinoma	24	8	p	n.l.	+	+	n.l.	+	n.l.	n.l.	+	+	+	n/a	n/a	n/a	+	n/a	improved
8	60	F	lung	carcinoma	–1	3	p	p	+	+	n.l.	n.l.	n.l.	n.l.	n.l.	+	n/a	n/a	n/a	+	+	n/a	not improved (death)
12	60	F	brest	carcinoma	3	10	p	n/a	+	n.l.	n.l.	+	n.l.	n.l.	+	+	n/a	n/a	n/a	n/a	n/a	n/a	improved
13	62	F	brest	carcinoma	2	5	p	p	+	+	n.l.	n.l.	+	+	n.l.	+	n/a	n/a	+	+	+	n/a	improved
14	63	F	brest	carcinoma	24	14	p	n/a	+	+	n.l.	n.l.	n.l.	+	n.l.	+	n/a	n/a	n/a	n/a	+	n/a	improved
15	64	F	lung	carcinoma	0	16	p	n/a	+	+	+	+	–	+	n.l.	+	n/a	n/a	n/a	n/a	+	chemotherapy (include rituximab)	improved
16	67	F	renal	carcinoma	0	10	p	n/a	+	+	n.l.	+	n.l.	n.l.	n.l.	+	n/a	+	n/a	n/a	n/a	n/a	improved
17	70	F	esopaghea	carcinoma	0	3	p	n	+	+	n.l.	n.l.	n.l.	n.l.	n.l.	+	n/a	n/a	n/a	n/a	+	n/a	improved
18	72	F	lung	carcinoma	–3	9	p	p	+	+	n.l.	n.l.	n.l.	n.l.	n.l.	+	n/a	+	n/a	n/a	n/a	n/a	improved
19	76	M	lung	carcinoma	0	20	p	n.l.	+	+	n.l.	+	n.l.	+	n.l.	+	n/a	+	n/a	n/a	n/a	n/a	not improved (death)
20	83	M	blood	hematological malignancy	–3	6	p	n.l.	+	n.l.	n.l.	n.l.	n.l.	n.l.	n.l.	+	n/a	n/a	+	n/a	+	chlorambucil	improved
21	85	F	stomach	carcinoma	0	10	p	p	+	+	+	+	–	+	–	+	n/a	+	n/a	n/a	+	n/a	improved
22	87	M	prostate	carcinoma	–2	4	p	n/a	n.l.	n.l.	+	n.l.	n.l.	n.l.	n.l.	+	n/a	n/a	n/a	n/a	n/a	n/a	not improved

NMOSD: Neuromyelitis Optica Spectrum Disorders, LETM: longitudinally extended transverse myelitis, AQP4: Anti-Aquaporin-4, Ab: antibody, EDSS: Expanded Disability Status Scale of Kurtzke, MRC: Medical Research Council, IVMP: intravenous methylprednisolone, IVIg: intravenous immunoglobulin, PE: plasma exchange, PLS: prednisolone, p: positive, n: negative, n/a: not applicable, n.l.: not listed.

Table 3 [Comparison of patients with any causes of NMOSD and those with cancer-associated NMOSD with LETM] Length of LETM might be longer in cases of cancer-associated NMOSD.

	Hu, et al.	Cancer-associated NMOSD with LETM
Female, n (%)		
Whole	248 (83.2)	20 (84.6)
EO-NMOSD	132 (80.5)	10 (100)
LO-NMOSD	116 (86.6)	12 (75.0)
Age of onset, year, mean (%)		
Whole	46.2 ± 15.1	54.08 ± 18.7
EO-NMOSD	35.4 ± 10.0 (55.0)	35.3 ± 9.73 (38.5)
LO-NMOSD	59.5 ± 7.9 (45.0)	66.9 ± 11.0 (61.5)
Death, n (%)		
Whole	7 (2.7)	2 (7.7)
EO-NMOSD	3 (1.8)	0 (0.0)
LO-NMOSD	4 (3.0)	2 (12.5)
Length of NMOSD, median (IQR)		
Whole	5.0 (3.0–8.0)	9.0 (5.0–12.8)
EO-NMOSD	6.0 (3.0–9.0)	6.0 (5.0–12.0)
LO-NMOSD	5.0 (3.0–7.0)	9.0 (5.0–13.0)

NMOSD: Neuromyelitis Optica Spectrum Disorders, LETM: longitudinally extended transverse myelitis, EO-NMOSD: early-onset of NMOSD, LO-NMOSD: late-onset NMOSD, LETM: longitudinally extended transverse myelitis.

onset of cancer and NMOSD (month), and length of LETM. However, these factors showed no significant association with outcome (Table 4).

In the previous review of patients with any causes of NMOSD, EDSS at last follow up were summarized as 2.5 in median value, and EDSS >6 in 22.2%, EDSS >8 in 8.7% and death in 2.3%[23]. This review did not describe mean or median EDSS at onset. Because most previous case reports do not have the description of EDSS of onset and last follow up, we could not examine the trend of recovery in cancer-associated NMOSD with LETM. There have been several case reports which showed remarkable or excellent to complete recovery from NMOSD[7][12]. Those cases and our case similarly had very long LETM, which extended beyond the average of LETM in cancer-associated NMOSD. Since length of LETM did not show association with outcome, length of LETM did not determine treatment responsiveness, including prognosis.

Cancer can be typically classified as carcinoma, sarcoma, or hematological malignancies. Although teratoma is a benign tumor, as a cause of paraneoplastic syndrome, we considered teratoma as a distinct type along with carcinoma, sarcoma, or hematological malignancies. There have been previous case reports of NMOSD with carcinoma, hematological malignancies, and teratoma, but there was no case report of sarcoma-associated NMOSD with LETM, although AQP4 is expressed on the fast twitch fibers of skeletal muscle[24]. Some of the tumor cells were identified to express AQP4[24]. A previous report showed anti-AQP4 antibody positive specimens in immunological staining. Although breast, thyroid, duodenum, and small intestine did not usually express AQP4[24], there have been case reports with positive immunostaining with anti-AQP4 antibody, in breast cancer[13], lung cancer[6][8][21], teratoma[1][7] and stomach cancer[19]. However, there was the case report of thyroid cancer with positive immunostaining by anti-AQP4, although normal thyroid tissue does not express AQP4[25]. Although most of the previous case reports showed single neurological event, there was a report of recurrent NMOSD which were accompanied by recurrence of cancer[26]. We could not find case reports of NMOSD associated with hematological malignancy based on immunostaining of its bone marrow. To assess the relationship between type of cancer and outcome of cancer-associated NMOSD with LETM, we may need additional case reports with immunostaining of tumor including bone marrow (We did not conduct immunostaining of the resected breast tumor tissue because of its high cost).

In conclusion, we experienced a case of NMOSD with 13

Table 4 [Factors and outcome in cancer-associated NMOSD with LETM]

		Improved, n (%)	Not improved and death, n (%)	*P* value (Fisher's exact test)
Cancer-associated NMOSD		22 (84.6)	4 (15.4)	***
Age of onset	EO-NMOSD	9 (34.1)	1 (3.8)	1
	LO-NMOSD	13 (50.0)	3 (11.5)	
Sex	Female	20 (76.9)	2 (7.7)	1
	Male	4 (14.5)	2 (7.7)	
Type of cancer	hematological malignancies	3 (11.5)	0 (0)	1
	carcinoma	15 (57.7)	4 (14.5)	
	teratoma	4 (15.4)	0 (0)	
Diagnostic interval between onset of cancer and NMOSD (month)	−12 to −7	2 (7.7)	0 (0)	0.72
	−6 to 0	12 (46.2)	3 (11.5)	
	1 to 6	4 (15.4)	1 (3.8)	
	7 to 12	2 (7.7)	0 (0)	
	13 to 18	0 (0)	0 (0)	
	19 to 24	2 (7.7)	0 (0)	
Length of LETM	3 to 5	6 (23.1)	2 (7.7)	0.85
	6 to 8	4 (15.4)	0 (0)	
	9 to 11	6 (23.1)	0 (0)	
	12 to 14	4 (15.4)	0 (0)	
	15 to 17	1 (3.8)	0 (0)	
	18 to 20	1 (3.8)	0 (0)	

In cancer-associated NMOSD with LETM, sex, type of cancer, diagnostic interval between onset of cancer and NMOSD (month) showed no association with outcome.
NMOSD: Neuromyelitis Optica Spectrum Disorders, LETM: longitudinally extended transverse myelitis, EO-NMOSD: early-onset of NMOSD, LO-NMOSD: late-onset NMOSD, LETM: longitudinally extended transverse myelitis

vertebrae length LETM which was developed after breast cancer. This case had good response to combination therapy, including IVMP, IVIg, PE, and PSL. We used these treatment modalities since these were used for typical NMOSD in previous reports, and the patients had good recovery. Our literature review was not able to find out relationship between sex, type of cancer, and diagnostic interval between onset of cancer and NMOSD (month). To scrutinize the relationship between clinical factors and outcome, we need to examine more case reports or case series with detailed description.

References

1) Bernard-Valnet R, Cobo-Calvo A, Siegfried A, et al. Paraneoplastic neuromyelitis optica and ovarian teratoma: a case series. Mult Scler Relat Disord 2019;31:97-100.
2) Blackburn K, Wang C, Greenberg B. Two cases of aquaporin-4 positive neuromyelitis optica associated with T-cell lymphoma. J Neuroimmunol 2020;338:577092.
3) Jin H, Hao H, Nan D, et al. Neuromyelitis optica spectrum disorder coincident with renal clear cell carcinoma: a case report. Medicine 2019;98:e14229.
4) Carrillo P, Gorría T, Santana D, et al. Aquaporin-4-positive triple-negative breast cancer presenting with paraneoplastic neuromyelitis optica spectrum disorder. Biomed Hub 2022;7:11-16.
5) Etemadifar M, Nikanpour Y, Neshatfar A, et al. Paraneoplastic neuromyelitis optica associated with zxsfever of unknown origin as an early manifestation: a case report. Mult Scler Relat Disord 2019;27:200-202.
6) Baik KW, Kim SH, Shin HY. Paraneoplastic neuromyelitis optica associated with lung adenocarcinoma in a young woman. J Clin Neurol 2018;14:246-247.
7) Frasquet M, Bataller L, Torres-Vega E, et al. Longitudinally extensive transverse myelitis with AQP4 antibodies revealing

ovarian teratoma. J Neuroimmunol 2013;263:145-147.
8) Apiraksattaykul N, Songwisit S, Owattanapanich W, et al. AQP4-IgG-positive neuromyelitis optica spectrum disorder and temporally detected neoplasms: case report and systematic review. Mult Scler Relat Disord 2022;68:104212.
9) Zoccarato M, Saddi MV, Serra G, et al. Aquaporin-4 antibody neuromyelitis optica following anti-NMDA receptor encephalitis. J Neurol 2013;260:3185-3187.
10) Beauchemin P, Iorio R, Traboulsee AL, et al. Paraneoplastic neuromyelitis optica spectrum disorder: a singlep center cohort description with two cases of histological validation. Mult Scler Relat Disord 2018;20:37-42.
11) Ding M, Lang Y, Cui L. AQP4-IgG positive paraneoplastic NMOSD: a case report and review. Brain Behav 2021;11:e2282.
12) Yuan J, Jia Z, Qin W, et al. Paraneoplastic neuromyelitis optica spectrum disorder associated with breast cancer. Clin Interv Aging 2019;14:1039-1044.
13) Armağan H, Tüzün E, Içöz S, et al. Long extensive transverse myelitis associated with aquaporin-4 antibody and breast cancer: Favorable response to cancer treatment. J Spinal Cord Med 2012;35:267-269.
14) Mueller S, Dubal DB, Josephson SA. A case of paraneoplastic myelopathy associated with the neuromyelitis optica antibody. Nat Clin Pract Neurol 2008;4:284-288.
15) Deuel LM, Bunch ME. A case of paraneoplastic neuromyelitis optica associated with small cell lung carcinoma. J Neuroimmunol 2018;316:130-132.
16) Mahale R, Mehta A, Buddaraju K, et al. Longitudinally extensive transverse myelitis with aquaporin-4 antibody positivity in renal cell carcinoma: rare occurrence. Neurol India 2019;67:1087-1089.
17) Kon T, Ueno T, Suzuki C, et al. Aquaporin-4 antibody positive neuromyelitis optica spectrum disorder associated with esophageal cancer. J Neuroimmunol 2017;309:38-40.
18) Wang SSY, Lau TKH. Paraneoplastic neuromyelitis optica spectrum disorder diagnosed with mantle cell lymphoma. Hong Kong Med J 2018;24:637-638.
19) Takewaki D, Kasai T, Itoh K, et al. Case of neuromyelitis optica with recurrent stomach carcinoma. Clin Exp Neuroimmunol 2017;8:327-330.
20) Kitazawa Y, Warabi Y, Bandoh M, et al. Elderly-onset neuromyelitis optica which developed after the diagnosis of prostate adenocarcinoma and relapsed after a 23-valent pneumococcal polysaccharide vaccination. Intern Med 2012;51:103-107.
21) Iorio R, Rindi G, Erra C, et al. Neuromyelitis optica spectrum disorder as a paraneoplastic manifestation of lung adenocarcinoma expressing aquaporin-4. Mult Scler 2015;21:791-794.
22) Eba S, Nishiyama S, Notsuda H, et al. Development of paraneoplastic neuromyelitis optica after lung resection in a patient with squamous cell carcinoma. Ann Thorac Cardiovasc Surg 2023;29:49-52.
23) Hu Y, Sun Q, Yi F, et al. Age of onset correlates with clinical characteristics and prognostic outcomes in neuromyelitis optica spectrum disorder. Front Immunol 2022;13:1056944.
24) Verkman AS, Anderson MO, Papadopoulos MC. Aquaporins: important but elusive drug targets. Nat Rev Drug Discov 2014;13:259-277.
25) Soelberg K, Larsen SR, Moerch MT, et al. Aquaporin-4 IgG autoimmune syndrome and immunoreactivity associated with thyroid cancer. Neuroimmunol Neuroinflamm 2016;3:e252.
26) Ontaneda D, Fox RJ. Is neuromyelitis optica with advanced age of onset a paraneoplastic disorder? Int J Neurosci 2014;124:509-511.

Acknowledgments：We wish to thank Eiko Shimabukuro, out dear librarian. Also, we wish to thank Rei Makishi, the husband of Naoko Makishi, who fully supports our first author.
Ethical statement：We gained informed consent for this report from the patient.
COI：The authors declare that there is no conflict of interest relevant to this article.
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