8ª Giornata dello specializzando in Neurologia - *Catania, 11 giugno 2019*

ANTI-RI-ASSOCIATED PARANEOPLASTIC OPHTALMOPLEGIA-ATAXIA SYNDROME IN A WOMAN WITH BREAST CANCER

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Review

Lancet Neurol 2010; 9: 94–104

Sporadic ataxia with adult onset: classification and diagnostic criteria

Thomas Klockgether

	Associated cancer	Other paraneoplastic syndromes
Anti-Yo (PCA-1)	Gynaecological, breast	..
Anti-Hu (ANNA-1)	SCLC	PEM, PSN
Anti-Tr	Hodgkin's lymphoma	..
Anti-Ri (ANNA-2)	SCLC, gynaecological, breast	Opsoclonus myoclonus syndrome
Anti-mGluR1	Hodgkin's lymphoma	..
Anti-CV2 (CRMP5)	SCLC, thymoma	PEM
Anti-ZIC4	SCLC	..
Anti-VGCC	SCLC	LEMS

Adapted from Dalmau and Rosenfeld,[35] with permission from Elsevier. ANNA-1/2=anti-neuronal nuclear antibody type 1/2. CRMP5=collapsin response mediator protein 5. LEMS=Lambert–Eaton myasthenic syndrome. mGluR1=metabotropic glutamate receptor type 1. PCA1=Purkinje cell antibody type 1. PEM=paraneoplastic encephalomyelitis. PSN=paraneoplastic sensory neuropathy. SCLC=small-cell lung cancer. VGCC=voltage-gated calcium channel. ZIC4=zinc finger protein 4.

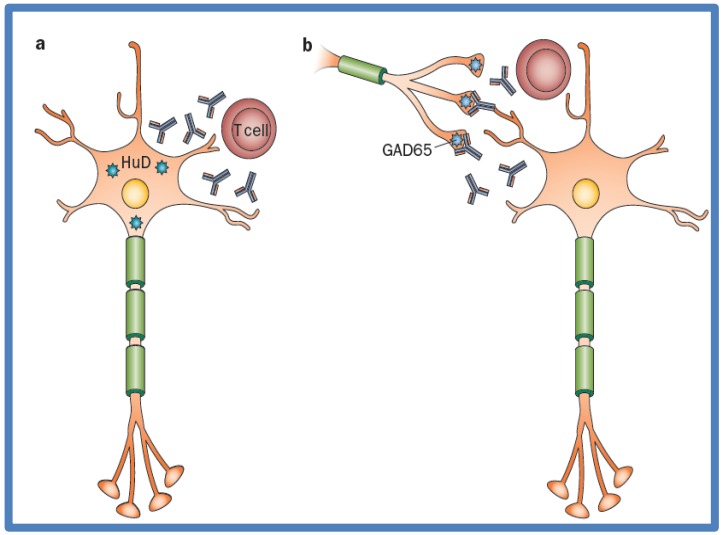
Table 1: **Autoantibodies in paraneoplastic cerebellar degeneration**

nature REVIEWS NEUROLOGY
2012; 8:380-390

Neuronal autoantigens—pathogenesis, associated disorders and antibody testing

Eric Lancaster and Josep Dalmau

Antibodies to intracellular antigens



T-cell mediated mechanisms

Table 1 | Neuronal nonsynaptic autoantibody targets and associated syndromes

Antigen	Antigen function	Tumour association	Syndromes	Mechanisms	Prognosis
Hu proteins (primarily HuD, but also HuC, Hel-N1 and Hel-N2)[112]	HuD is important for neuronal RNA handling, cell-cycle regulation and cell development[113,114]	Small-cell lung cancer[115]	Neuropathy (often purely sensory), cerebellitis, limbic encephalitis, autonomic dysfunction and/or brainstem encephalitis	Antibodies are not directly pathogenic; possibly T-cell-mediated	20% survival at 3 years (encephalitis is slightly more likely to cause death than is cancer)
Collapsin response mediator protein 5	Regulation of neurite outgrowth, and neurogenesis[116]	Small-cell lung cancer and thymoma[117]	Neuropathy, uveoretinal symptoms, ataxia or limbic encephalitis[117]	Possibly T-cell-mediated[22]	Longer survival than with anti-Hu syndromes (48 versus 11 months)[117]
Ma1[118]	Promotion of apoptosis	Diverse (lung, skin, gastrointestinal and renal)	Limbic encephalitis, cerebellitis, brainstem encephalitis or polyneuropathy	Probably T-cell-mediated rather than antibody-mediated[21]	In a series of 13 patients, nine deteriorated, three stabilized and one improved[119]
Ma2 (also known as Ta)[118]	Not known	Germ cell tumours (especially in young men)	Limbic encephalitis, brainstem encephalitis, polyneuropathy or cerebellitis[119]	Not known	In a case series 33% improved, 21% stabilized and 46% deteriorated[119]
Yo proteins (also known CDR1 and CDR2)	CDR1 is strongly expressed in Purkinje cells; function unknown[120] CDR2 may be involved in cell cycle regulation, mitosis, and transcriptional regulation[121]	Specific to women Almost all are eventually diagnosed with breast or gynaecological cancer[122]	Paraneoplastic cerebellar degeneration	Conflicting data in patients regarding a role for T cells[27,28] Antibodies trigger neuronal cell death in slice culture[29]	Tumours may respond, but neurological symptoms are often unresponsive[122]
Ri proteins (also known as Nova-1 and Nova-2)	Nova-1 is an RNA-binding protein expressed by subcortical neurons Function of Nova-2 is not known	Breast cancer	Nova-1: cerebellar degeneration, encephalitis, myelitis, opsoclonus myoclonus[123,124] Nova-2: paraneoplastic opsoclonus myoclonus ataxia,[125] myoclonus, encephalitis, cerebellar degeneration and myelitis	Antibodies may prevent binding of Nova-1 to RNA[126] Unclear whether antibodies are pathogenic; comorbid antibodies are common and can occur in asymptomatic cancer patients[127]	Three of six patients improved; median survival >69 months in one series[123]
Tr	Found in Purkinje neurons;[128] function not known	Hodgkin lymphoma	Paraneoplastic cerebellar degeneration[129]	Not known	Relatively good: median survival >113 months[123]
Zinc finger protein ZIC 4	Important for brain development	Small-cell lung cancer	Paraneoplastic cerebellar degeneration[130]	Antibodies may not be pathogenic; 80% of patients have other antibodies as well	Not known
Gephyrin and GABARAP	Associated with GABAergic transmission	Gephyrin: mediastinal carcinoma GABARAP: not known	Stiff-person syndrome[131,132]	Not known	Not known

Abbreviations: GABA, γ-aminobutyric acid; GABARAP, GABA receptor-associated protein.

Case Report

- The patient is a 72-year-old right-handed woman with a three-month history of **blurred vision, diplopia and progressive gait disturbance.**
- Family history was negative for neurological disorder.
- She was also on therapy for arterial hypertension and type 2 (non-insulin-dependent) diabetes mellitus.

Neurological Examination

Severe gait and truncal ataxia

Pupillary responses were normal

Asymmetric bilateral horizontal gaze paresis, left worse than right

Horizontal nystagmus

Laboratory findings

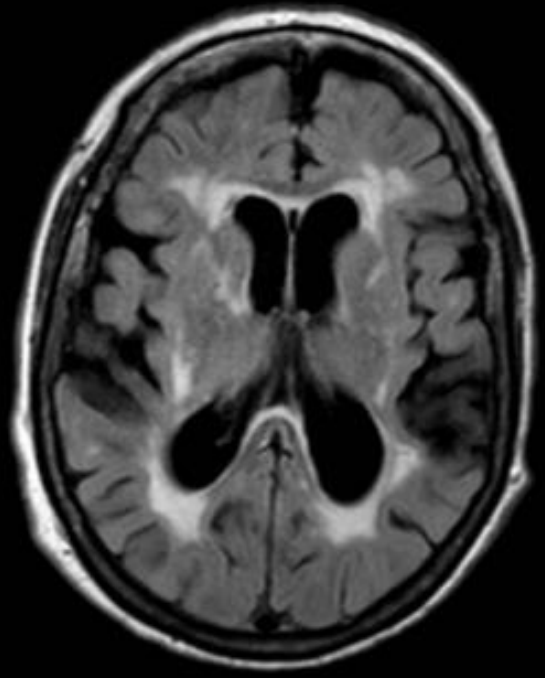
✓ Normal routine hematological and biochemical investigations, as well as serum blood gases, ammonia, vitamin B12, folate.

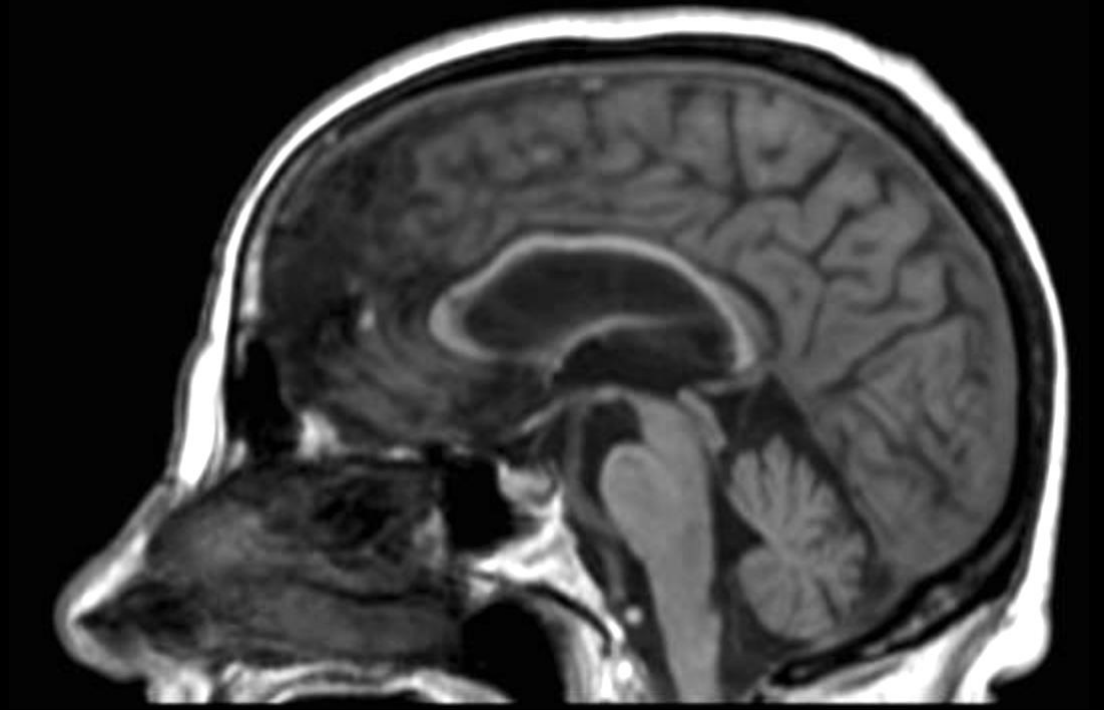
✓ Normal urinalysis.

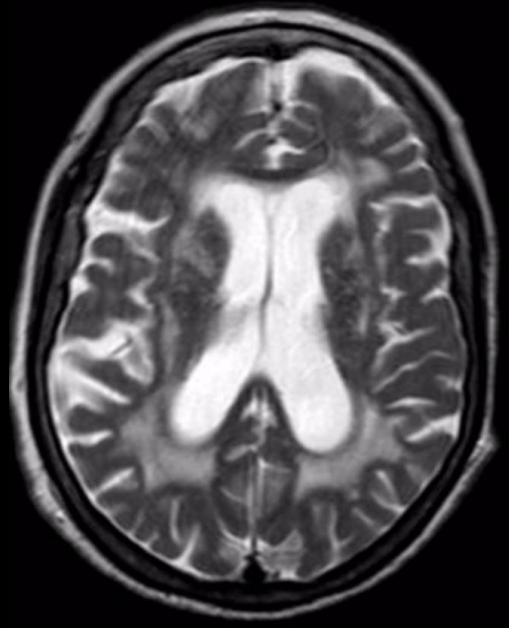
✓ Negative screen for anti-nuclear, anti-DNA, anti-mitochondrial, anti-microsomal, anti-endomysial, and anti-gliadin autoantibodies.

Cerebrospinal fluid examination →

- Mild lymphocytic pleocytosis (30 cells/mm^3)
- Positive oligoclonal bands







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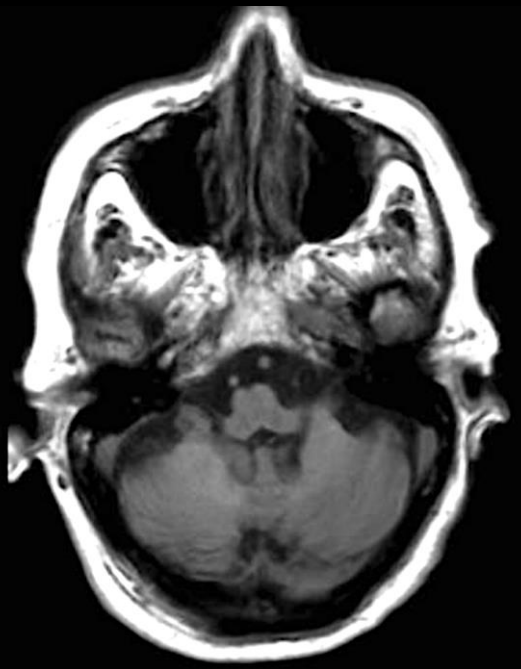
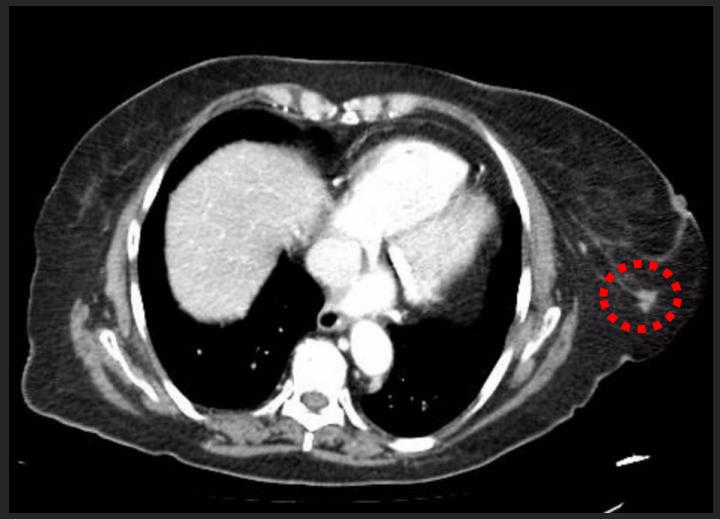
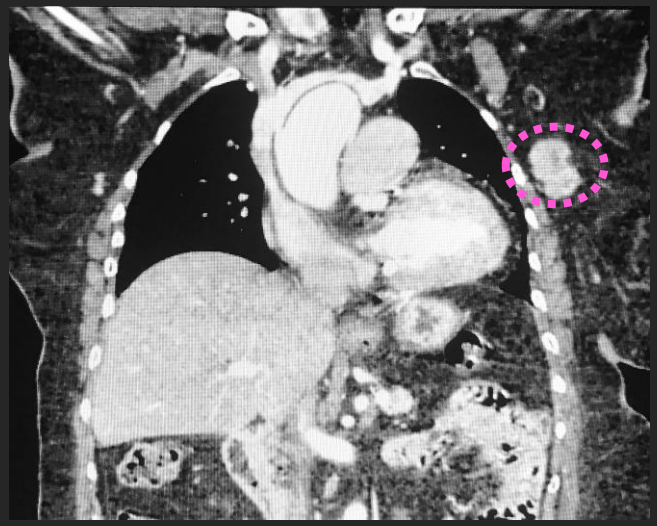


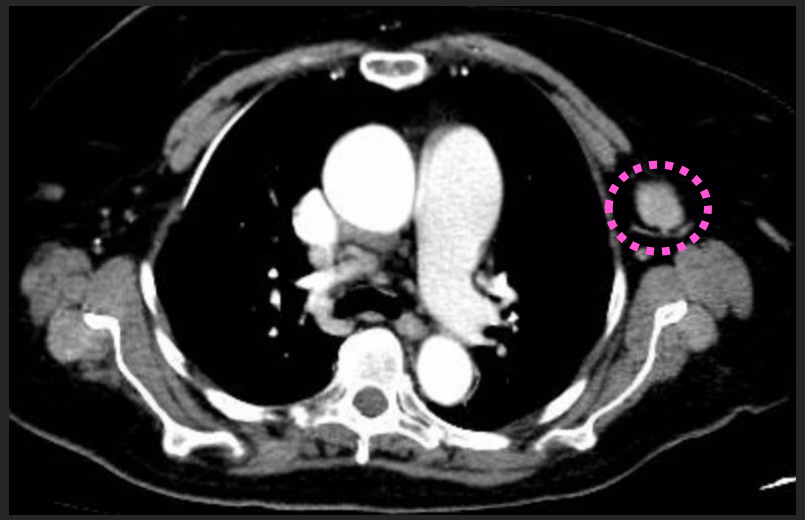
Whole-Body CT scan

Left nipple nodule



Left axillary adenopathy





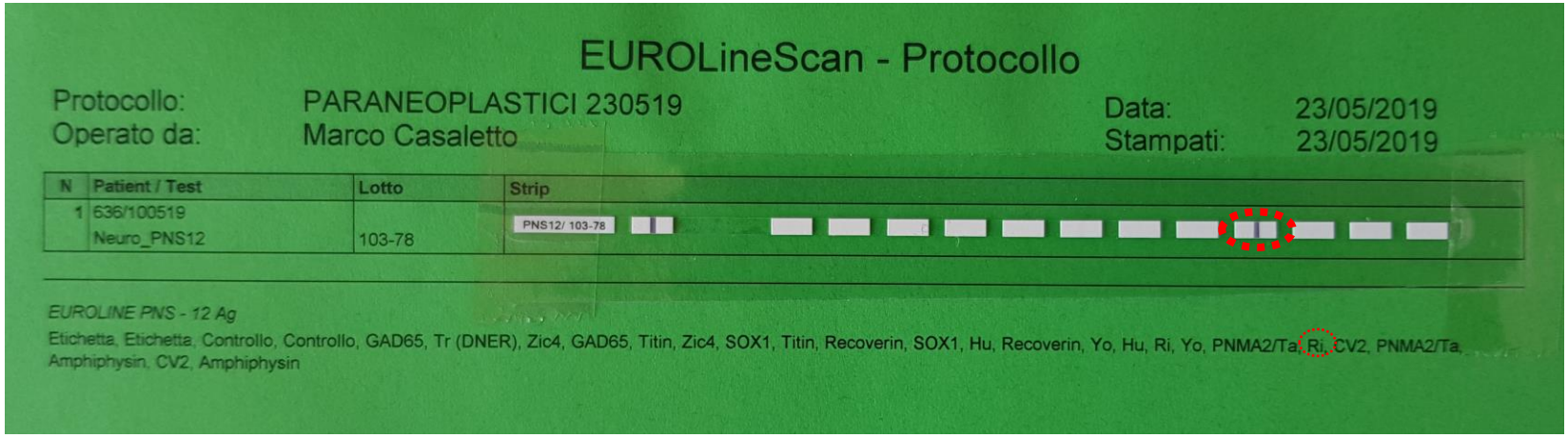
Echo-guided biopsy of the axillary node confirmed lymph node metastasis and she underwent a **breast-conserving surgery**, lumpectomy with left axillary node dissection.

Onconeural antibodies

ESAME: ANTICORPI PARANEOPLASTICI (Amfifisina,CV2,PNMA2/Ta,Ri,Yo,Hu,Recoverina,SOX1,Titina,Zic4,GAD65,Tr (DNER))

		INTENSITA'	CLASSE	RISULTATO
RISPOSTA:	ANTI Amfifisina	0	0	NEGATIVO
	ANTI CV2	0	0	NEGATIVO
	ANTI PNMA2/Ta	0	0	NEGATIVO
	ANTI Ri	107	+++	POSITIVO
	ANTI Yo	1	0	NEGATIVO
	ANTI Hu	0	0	NEGATIVO
	ANTI Recoverina	4	0	NEGATIVO
	ANTI SOX 1	1	0	NEGATIVO
	ANTI Titina	3	0	NEGATIVO
	ANTI ZIC 4	0	0	NEGATIVO
	ANTI GAD 65	0	0	NEGATIVO
	ANTI Tr (DNER)	3	0	NEGATIVO

INTENSITA'	CLASSE	RISULTATO
0-5	0	NEGATIVO
5-10	(+)	BORDERLINE
10-25	+	POSITIVO
25-50	++	POSITIVO
50-100	+++	POSITIVO



ORIGINAL ARTICLES

Ann Neurol 1991;29:241–251

Anti-Ri: An Antibody Associated with Paraneoplastic Opsoclonus and Breast Cancer

F. Antonio Luque, MD, PhD,*‡ Henry M. Furneaux, PhD,*‡ Reuven Ferziger, AB,*‡ Marc K. Rosenblum, MD,† Shirley H. Wray, MD, PhD,§ S. Clifford Schold, Jr, MD,¶ Michael J. Glantz, MD,¶ Kurt A. Jaeckle, MD,** Haim Biran, MD,†† Martin Lesser, MD,‡‡ William A. Paulsen, MD,§§ Mary E. River, MD,¶¶ and Jerome B. Posner, MD*‡

Table 1: Clinical Characteristics of Anti-Ri–positive Patients

Patient	Age (yr)	Time From Neurological Diagnosis to Tumor Diagnosis (mo.)	Oculomotor Disorder	Ataxia		Other Symptoms and Signs	Tumor Diagnosis
				Appendicular	Truncal		
1	60	−2	Opsoclonus	+	+	Dizziness, nausea	Breast, 1986
2	70	+108	Nystagmus; abnormal pursuit	−	+	Nausea	Breast, 1978
3	47	+9	Opsoclonus	−	+ (severe)	Dizziness, nausea	Breast, Stage I, 1983
4	55	−2	None	+	+ (moderate)	Dysesthesias, proximal muscle weakness	Breast (Stage II-III), 1986
5	58	0.5	Opsoclonus rotatory nystagmus, 6th nerve palsies	+ (severe)	+ (severe)	Spastic quadriparesis; hyperreflexic, decreased hearing, right ear; swallowing difficulty	Axillary, 1988
6	73	No tumor	Opsoclonus?; nystagmus; ocular flutter	+ (moderate)	−	Dizziness, occasional diplopia, dysarthria, dementia, cerebral and cerebellar atrophy on MRI	None
7	62	+1	Opsoclonus	−	+	Dizziness, nausea	Fallopian tube, 1989
8	61	−5	Opsoclonus	+	+	Dizziness, blepharospasm	Breast, 1983

DOI: 10.1093/brain/awg133 Advanced Access publication April 8, 2003 *Brain* (2003), **126**, 1409–1418

Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients

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Table 2 *Main clinical syndromes at presentation and high titre (≥400) paraneoplastic antineuronal autoantibodies detected over a 12-year period (1989–2001)*

Antibody	*n*	PCD (%)	PSN	PLE	PEM	POM	SPS
Anti-Hu	90	16 (18)	46	14	13	1	–
Anti-Yo	19	19 (100)	–	–	–	–	–
Anti-Tr	7	7 (100)	–	–	–	–	–
Anti-Ri	7	6 (86)	–	–	–	1	–
Anti-amphiphysin	7	–	4	1	1	–	1
Anti-CV2	5	–	3	1	1	–	–
Anti-mGluR1	2	2 (100)	–	–	–	–	–
Total	137	50 (37)	53	16	15	2	1

PSN = paraneoplastic sensory neuropathy; PLE = paraneoplastic limbic encephalitis; PEM = paraneoplastic encephalomyelitis; POM = paraneoplastic opsoclonus/myoclonus; SPS = stiff person syndrome.

Table 4 *Associated tumours in 50 PCD patients*

Antibody	*n*	Lung	Gynaecological	Breast	Hodgkin's	Other	No tumour
Anti-Yo	19	–	9	3	–	3	4
Anti-Hu	16	14	–	–	–	–	2
Anti-Tr	7	–	–	–	6	–	1
Anti-Ri	6	–	1	3	–	1	1
Anti-mGluR1	2	–	–	–	2	–	–
Total	50	14	10	6	8	4	8

Conclusion

- The present case further illustrates that recognition of PNS is important, since neurological symptoms almost invariably predate direct symptoms of the primary tumor, and **treatment at early stages** may provide better chance of good outcome.
- The presence of **anti-Ri antibody** typically identifies **women with opsoclonus/myoclonus and ataxia** who usually suffer from breast cancer.
- We have now illustrated the occurrence of **anti-Ri even in the absence of opsoclonus**, thus enlarging its clinical spectrum.
- In this way, our findings further reinforce the belief that **opsoclonus/myoclonus cannot be considered** syndromic of anti-Ri-antibody-associated paraneoplastic syndrome.

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THANK YOU FOR YOUR ATTENTION