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ORIGINAL ARTICLE

Paraneoplastic neurological syndromes of the central nervous system: a single institution 7-year case series

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Abstract

Background Paraneoplastic neurological syndromes (PNSs) are nonmetastatic complications of malignancy, defined by the presence of onconeural antibodies (ONAs). ONAs may be found in 60% of patients with central nervous system (CNS) involvement, and they are directed against intraneuronal antigens or channels, receptors or associated proteins located at the synaptic or extra-synaptic neuronal cell membrane. Given its rare incidence, there are few epidemiological case series on CNS-PNS. We aim to discuss the variability of CNS-PNSs etiology, clinical features, management and outcome, highlighting the importance of early recognition and appropriate treatment, leading to significant reduction of mortality and morbidity.

Methods We retrospectively reviewed our 7-years single-center experience, and specifically discussed the underlying etiology, parenchymal CNS involvement, and the acute treatment response. Only cases fulfilling PNS Euronetwork criteria for definitive PNS were included.

Results A total of 26 probable PNSs cases involving CNS were identified. We reported medical records of eleven (42.3%) illustrative cases, meeting the criteria of definite PNS and presenting variable clinical spectrum and different radiological appearances. Our series has a relative paucity of the most common syndromes and larger portion of clinical diagnosis with ONAs. Well-characterized ONAs had been detected in CSF of six patients.

Conclusions Our case series supports the utmost importance of early recognition of CNS-PNSs. Screening for occult malignancies should not be limited to patients with classical CNS syndrome. Empiric immunomodulatory therapy may be considered before the diagnostic evaluation is completed, in order to prevent unfavorable outcome. Late presentations should not discourage initiation of treatment.

Keywords CNS paraneoplastic neurological syndrome · Classical and non-classical syndromes · Well- and partially-characterized onconeural antibodies · Immunotherapy

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Introduction

Paraneoplastic neurologic syndromes (PNSs) are a group of disorders resulting from a remote effect of a malignant neoplasm. PNSs may involve any part of the nervous system and result from an immune-mediated mechanism affecting neural tissue with a direct damage, rather than the direct or metastatic invasion of cancer [1]. Neuronal death could depend on autoreactive T cells, and actually, it has been hypothesized that the tumor protein-targeting immune response might attack the same protein expressed by neurons [2]. PNSs are clinically characterized by subacute progression, disability, substantial lack of response to therapies, and they may precede clinical signs and symptoms of the underlying tumor in 65% of the cases. The heterogeneity of PNSs reflects the distribution of onconeural antigens within the nervous system, and therefore central, peripheral, and autonomic nervous systems can be affected at various levels. The identification of intracellular antigens, targeting B-cell immune response, allowed to identify the link between cancer and PNS, and subsequently to develop diagnostic tests [2]. Two different patterns of immune response may accompany PNSs: syndromes in which immunoreactivity is directed against neuronal receptors or other cell membrane antigens, and syndromes with an immune response directed against intra-cellular neuronal proteins [3]. PNSs are defined by the presence of onconeural antibodies (ONAs), which are classically directed against intracellular-neuronal antigens, but may also target channels, receptors or associated proteins located at the synaptic or extra-synaptic neuronal cell membrane. The ONAs are detected in about 60% of patients with PNS of the central nervous system (CNS) and less than 20% of those affecting the peripheral nervous system. Therefore, ONAs finding in patients with a progressive neurological disease supports the diagnosis of PNS and may provide information about the nature of a supposed underlying tumor, but their absence does not exclude the diagnosis of PNS [1, 2]. Although there is significant overlap, many of these antibodies (abs) are specific to one or more clinical syndromes and tumor types, suggesting the potential site of an underlying cancer. Not all paraneoplastic abs have the same sensitivity and specificity, hence they can be classified in two categories according to their clinical relevance: "well characterized abs" and "partially characterized abs" [4]. Similarly, clinical syndromes can be divided into those with a high probability of paraneoplastic etiology and those less likely associated with underlying cancer, termed "classical" and "non-classical syndromes" respectively [1, 2, 5]. The purpose of this paper is to provide clinicians with an insight into different clinical scenarios of PNSs, in order to highlight the importance of early recognition and appropriate treatment, leading to significant reduction of mortality and morbidity. Hence, we reported our single-center experience, and presented illustrative cases of PNSs involving CNS, with variable clinical spectrum and different radiological appearances. Addressing with this subject, we specifically discuss the underlying etiology, parenchymal CNS involvement, and the acute treatment response, in order to compare and contrast the variability of their etiology, clinical features, management and outcome.

Methods

We compiled a consecutive case series by searching the quality control database of the Neurology Department (ND) at Polyclinic Hospital of Messina, for PNS cases involving CNS, and first ever reported between 2015 and 2022. The following search terms were used: ICD-9 code 323.9 [unspecified causes of encephalitis, myelitis and encephalomyelitis (EM)], 'paraneoplastic', 'limbic', 'encephalitis', 'rhombencephalitis', 'optic neuritis'. Long-term follow-up results were used to definitively classify possible or probable PNS. We based diagnosis on the algorithm proposed by Graus et al. [4].

Only cases fulfilling PNS Euronetwork criteria [4] for definitive PNS were included. These include patients with a neurologic syndrome and well-characterized ONAs (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, anti-amphiphysin); with CNS classical syndromes [encephalomyelitis, paraneoplastic limbic encephalitis (LE), subacute cerebellar degeneration (SCD), opsoclonus–myoclonus syndrome (OMS)] who developed cancer within 5 years; with a CNS nonclassical syndrome [brainstem encephalitis (BE), optic neuritis (ON), necrotizing myelitis/myelopathy, and stiff-person syndrome (SPS) and variants] that substantially improves after cancer treatment; or a non-classical syndrome with ONAs who developed cancer within 5 years. Patients with overlap syndromes were classified based on their predominant neurologic findings. Sensitivity of diagnostic investigations [magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis] was calculated.

Results

Patient population

A total of 26 probable PNSs cases involving CNS were identified. Eleven cases (42.3%) met the criteria of definite PNS. The median age at onset was 63 (range 32–80), with a male to female ratio of 1:2.66. A larger portion of patients (7/11) lacked a known neoplasm at syndrome onset. A new

diagnosis of neoplasm or metastatic disease was established in ten patients. One patient with definite PNS has not developed detectable neoplasia to date.

Fifteen cases were excluded because we were unable to establish a definitive diagnosis. Five of these patients were excluded because of incomplete information.

Neurologic syndromes, ONAs and neoplasms

The spectrum of neurologic syndromes included: LE with or without extralimbic involvement (45.5%, 5/11), SCD (18.2%, 2/11), OMS (9.1%, 1/11), BE (18.2%, 2/11), SPS with cerebellar ataxia (9.1%, 1/11), peripheral neuropathy (2/10) and neuromuscular junction disorder (1/10). One patient had extralimbic encephalitis (ELE) alone. The median time from symptom onset to hospital admission or neuro-oncologic consultation was 7 months (range = 0–144 months; n = 11). Nearly all cases (72.7%, 8/11) presented less than 12 months after symptom onset with a rapidly progressive course. ONAs were identified in 90.9% of cases (10/11): anti-Hu (two cases), anti-Ma (two), anti-SOX1 (two) and one each of anti-Yo, anti-Zic4, anti-CV2/CRMP, anti-GAD65, and anti-CASPR-2. In one case, two ONAs were found (anti-Hu plus anti-SOX1). All the ONA were detected in the serum and in the CSF. The following tumors were identified: lung cancer (4/11, 36.4%), including small cell lung cancer (SCLC), non-SCLC (NSCLC), pulmonary neuroendocrine tumor (PNT), and primary lung lymphoma (PLL); lymphoproliferative disorders (2/11, 18.2%); mammary adenocarcinoma (MAC, 1/11); seminomatous germ-cell testicular tumor (SGCTT, 1/11), transitional cell carcinoma (TCC) of the bladder (1/11), and one case of basaloid squamous cell carcinoma (BSCC) of the anus. Table 1 summarizes salient points in terms of diagnostic modalities used, reporting clinical, laboratory and radiological features of patients identified in our cohort. Table 2 details each case listing the identified PNSs and related ONAs, the associated neoplasms with stage at diagnosis, immunotherapy and response to treatment, disease course, data about time between symptoms onset and presentation at ND, and outcomes over time.

We assigned collected data to three laboratory level scenarios, considering both high-risk (classical syndromes) and intermediate-risk phenotypes (non-classical syndromes), respectively.

Scenario 1 – Well-characterized ONAs

Case 1. A 63-year-old female was admitted to ND for dysphagia, progressive visual symptoms, and gait impairment. The patient reported, moreover, episodes characterized by sudden loss of contact with the environment, marked asthenia and loss of muscle tone lasting a few seconds. She had personal history of bilateral MAC, treated with surgery and radiotherapy twenty years before, and colorectal adenocarcinoma, treated with surgery and chemotherapy four years before, without recurrence at follow-up. Neurological assessment of the bedridden patient revealed rotational nystagmus and diplopia in all directions of gaze, mixed dysphagia, severe limb muscle wasting, and areflexia of upper limbs. Routine investigation including complete blood count, renal and liver function test, viral and tumor markers, urine microscopy was within normal limit. Whole-body (WB) computed tomography (CT) and positron emission tomography (PET) revealed three bilateral lung nodules, mediastinal adenopathy and hepatic lesion 7 mm. Brain MRI showed limbic and extralimbic involvement (online Fig. 1A). CSF cytology showed normal cell count with normal protein and serum–CSF glucose ratio. The search of ONAs revealed well-characterized anti-**Ma2** abs in CSF. Intravenous methylprednisolone pulse (IvMP, 1 g/day) was given for 5 days followed by oral prednisolone 1 mg/kg. She started showing mild improvement in sight and gait, and in radiological follow-up (online Fig. 1B).

Case 2. A 32-year-old male, with personal history of psychoactive substance abuse and sexually-transmitted diseases (Chlamydia Trachomatis), presented diplopia and bilateral ptosis, occasional swallowing difficulty, and lower limb muscle fatigability. Neurological assessment in ND revealed combined vertical gaze ophthalmoplegia, dysphagia, and normal deep tendon reflexes. After suspecting myasthenia gravis, neurologists administered immunomodulatory and symptomatic treatment without improvement. CSF cytology showed an increased total protein concentration with normal total nucleated cell count. Suspecting Miller Fisher syndrome, the patient was treated with high-dose intravenous immunoglobulin (IvIg) therapy, but it was ineffective. Routine investigation including complete blood count, renal and liver function test, viral and tumor markers, urine microscopy was within normal limit, except for the detection of serum abs directed against Borrelia burgdorferi. MRI revealed involvement of both oculomotor nerves and the pontine tegmentum (Fig. 1A–C). The patient was discharged with antibiotic and steroid therapy. The patient presented neurological worsening at three months follow-up, showing complete ophthalmoplegia, ataxic gait, lethargy, and slurred speech. Repeated MRI (Fig. 1D–F) showed extension of lesion in the pons. Well-characterized anti-**Ma2** abs were revealed in CSF. A SGCTT was detected and treated with radical inguinal orchiectomy. Following three plasma exchange (PlEx) sessions, the patient was discharged with slight improvement in speech and gait. After three weeks, the patient was admitted again because of new worsening of symptoms, complaining of ophthalmoplegia, severe dysarthria and dysphagia. We started immunosuppressive therapy with Rituximab and administered a complete cycle of four 375 mg/kg – 1 day – 1 infusions. Unfortunately,

Table 1 Clinical, laboratory and radiological features of patients with CNS paraneoplastic neurological syndromes (PNSs) involving central nervous system (CNS) identified in our cohort

Patient	Sex	Age	Syndrome	Main clinical manifestation	Additional features	CSF analysis	Brain MRI
1	F	63	LE, ELE	Subacute dysphagia and gait impairment, focal seizures	Rotational nystagmus and severe muscolar atrophy	Normal	Normal at onset; during FU limbic and extralimbic involvement, with T2—FLAIR hyperintense signals in globus pallidus, thalamus, and the temporohippocampal and insular region on the left side
2	M	32	BE	Combined vertical gaze ophthalmoplegia, dysphagia, ataxic gait, lethargy, and slurred speech	Initial suspicion of MG and then MFS, detection of serum Abs directed against Borrelia burgdorferi	Increased total protein concentration with normal total nucleated cell count	Contrast enhancement of both oculomotor nerves, associated with a smooth long TR hyperintensity in the pontine tegmentum; during FU long-TR hyperintense signal in the pontine tegmentum more evident and extended
3	F	72	SCD	Gait ataxia, dysphagia, and slurred speech	Initial suspicion of SCA	Normal	Pontocerebellar atrophy with enlarged cisterna magna
4	F	47	ELE	Encephalopathy with GTCS and SE	Diffuse theta and delta waves, mixed with spikes	Normal	T2-FLAIR hyperintense signal in frontal and occipital lobes, mainly in the right side at onset; during FU decreased lobar involvement, but new long-TR hyperintense signal involving right basal ganglia and pulvinar
5	M	45	BE, LE, ELE	Dysphagia, mild dysarthria, and ataxic gait	EEG showed sporadic diffuse beta activity within a background of alpha rhythm	Normal	Brainstem, cerebellar, limbic and extralimbic involvement at different times, with T2—FLAIR hyperintense signals and contrast enhancement; during FU almost complete regression of long TR hyperintensities
6	F	64	LE	GTCS	Peripheral neuropathy and SIADH	Normal	T2/FLAIR hyperintense signal in left hippocampal-amygdala formation at onset; during FU mesial temporal lobe atrophic regression
7	F	75	LE	Fluent aphasia mimicking stroke	Behavior disturbances with agitation, hallucinations and cognitive decline	Normal	DWI-FLAIR hyperintense signals in parietal and temporoinsular region on the left side at onset; during FU reduction of long TR hyperintensities
8	M	67	SCD	Severe ataxic vermian and hemispheric syndrome, dysarthria	AChR negative MG/LEMS, and erectile dysfunction	Normal	T2 hyperhintense signal in cerebellar dentate nucleus and vermis; during FU marked cerebellar atrophy

Table 1 (continued)

Patient	Sex	Age	Syndrome	Main clinical manifestation	Additional features	CSF analysis	Brain MRI
9	F	78	OMS	Multidirectional saccadic eye movements (opsoclonus), involuntary muscle contractions (myoclonus), and truncal ataxia opsoclonus, moderate gait and limb ataxia associated with akinesia, tremor, rigidity, hyperreflexia	Seizures, cognitive impairment with persecutory and jealousy delusional thinking	Normal	DWI-FLAIR-T2 multiple chronic ischemic lesions in the periventricular and subcortical white matter
10	F	63	SPS	Limb plastic hypertonia and vermian ataxia	Rotational nystagmus, severe dysarthria, and dysdiadochokinesia in the upper limbs	Normal	FLAIR slight hyperhintense signal in the superior vermian cortex, associated with mild cerebellar and hippocampal atrophy
11	F	80	LE	Encephalopathy with delirium and SE	SIADH, peripheral neuropathy, EEG polymorphic theta-delta activity	Normal	FLAIR hyperintense lesion in the right temporal pole at onset; during FU long-TR hyperintense signal involving left parietal, right basal ganglia, right hippocampus, both thalami and median midbrain, and right temporal, perivascular spaces, and leptomeningeal contrast enhancement

Abs antibodies, *AChR* acetylcholine receptor, *BE* brainstem encephalitis, *CSF* cerebrospinal fluid, *DWI* diffusion-weighted imaging, *EEG* Electroencephalography, *ELE* extralimbic encephalitis, *FLAIR* Fluid-attenuated inversion recovery, *FU* follow-up, *GTCS* Generalized Tonic Clonic Seizures, *LE* limbic encephalitis, *LEMS* Lambert-Eaton myasthenic syndrome, *MG* myasthenia gravis, *MRI* magnetic resonance imaging, *MSF* Miller Fisher Syndrome, *mRS* modified Rankin Scale, *OMS* opsoclonus-myoclonus syndrome, *SE* status epilepticus, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *TR* repetition time

Table 2 Paraneoplastic neurological syndromes identified in our cohort, their associated onconeural antibodies and neoplasms with stage at diagnosis, immunotherapy and response to treatment, disease course, duration of neurological symptoms from onset to presentation at Neurology Department, and modified Rankin Scale at presentation and at the end of the follow-up

Patient	Sex	Age	Syndrome	Onconeural Abs	Cancer	Stage	Immune therapy	Response to treatment	Course	Time from symptom onset (months)	Presenting mRS	End of FU mRS
1	F	63	LE, ELE	Ma2	NSCLC	IV A	IvMP	Yes	Monophasic	5	4	3
2	M	32	BE	Ma2	SGCTT	0	IvIg, PlEx, RIX	Poor	Monophasic	9	4	5
3	F	72	SCD	Yo (PCA-1)	TCC of the bladder	Unknown	None	N/A	Relapsing	144	3	5
4	F	47	ELE	CV2/CRMP5	MAC	IV	Dex	Yes	Relapsing	0	5	5
5	M	45	BE, LE, ELE	Hu (ANNA 1)	/	/	IvMP	Yes	Monophasic	4	3	0
6	F	64	LE	Hu, SOX1	PNT	Extensive	Dex, VP-16	Poor	Monophasic	7	3	4
7	F	75	LE	SOX1	Basaloid SCC of the anus	III A	IvMP	Yes	Relapsing	48	4	3
8	M	67	SCD	Zic4	PLL	Advanced	Pr, AZA, Dex, EC	Yes	Monophasic	12	3	3
9	F	78	OMS	CASPR2	Mixed NSCLC-SCLC	III A	IvMP	Yes	Relapsing	24	5	6
10	F	63	SPS	GAD65	CD	II	IvIg, Pr. MTX	Yes	Monophasic	4	4	3
11	F	80	LE	/	CLL	B	Dex, IvMP, IBR	Yes	Relapsing	2	3	6

Abs antibodies, *ANNA* antineuronal nuclear antibody, *AZA* azathioprine, *BE*, brainstem encephalitis, *CASPR2* contactin-associated protein 2, *CD* Castleman's disease, *CLL* Chronic lymphocytic leukaemia, *CV2/CRMP5* collapsin response-mediator protein 5, *Dex* dexamethasone, *EC* etoposide-carboplatin, *ELE*, extralimbic encephalitis, FU follow-up, *GAD65* glutamic acid decarboxylase 65, *IBR* ibrutinib, IvIg intravenous immunoglobulin, *IvMP* intravenous methylprednisolone pulse, *LE* limbic encephalitis, *MAC* mammary adenocarcinoma, *MG*, myasthenia gravis, *mRS* modified Rankin Scale, *MTX* methotrexate, *N/A* not applicable, *NSCLC* non–small-cell lung cancer, *OMS* opsoclonus-myoclonus syndrome, *PCA-1* Purkinje cell antibody 1, *PlEx* plasma exchange, *PLL* primary lung lymphoma, *PNT* pulmonary neuroendocrine tumor, Pr prednisone, SCC squamous cell carcinoma, SCD subacute cerebellar degeneration, *SCLC*, small-cell lung cancer, *SGCTT*, seminomatous germ-cell testicular tumor, *SOX 1*, Anti-Sry-like high mobility group box 1, *SPS* stiff-person syndrome, *TCC* transitional cell carcinoma, *VP-16* etoposide, *Zic4* zinc finger protein 4

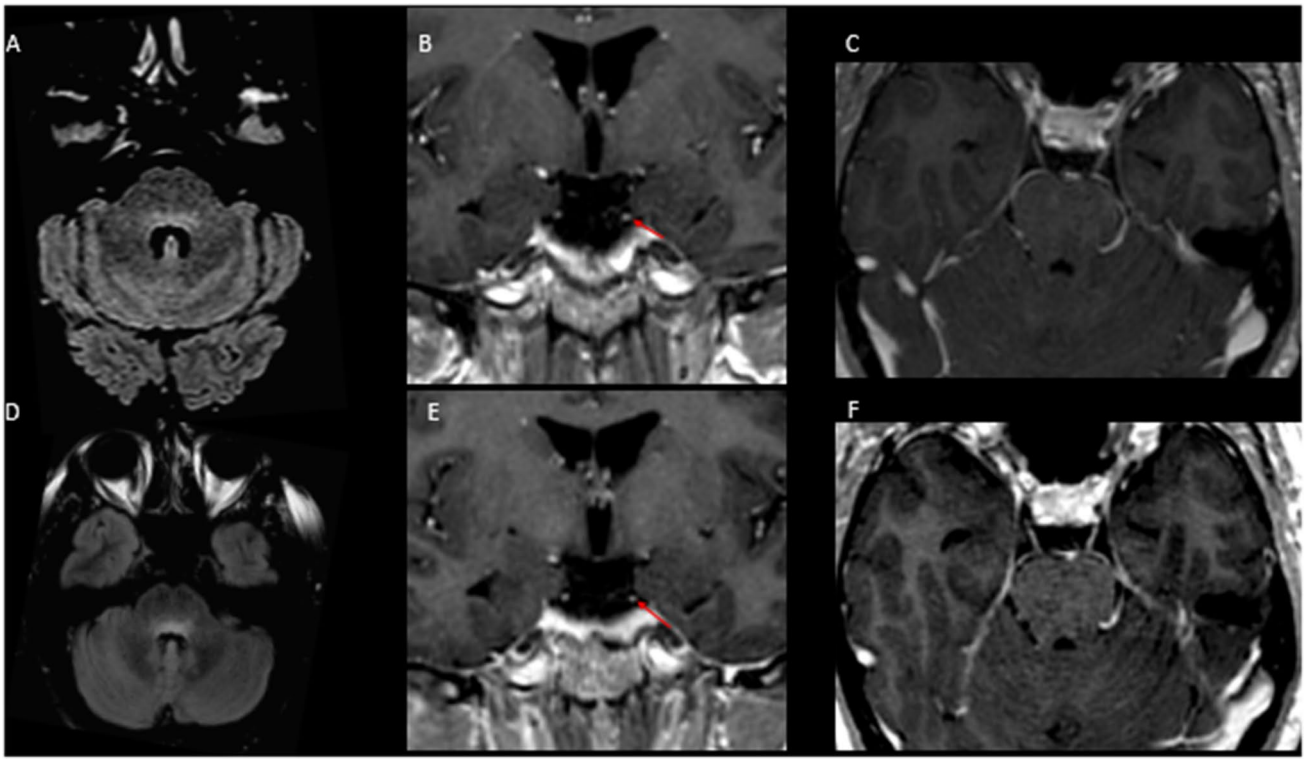

Fig. 1 Case 2. Brainstem encephalitis associated with anti-Ma2 abs and testicular seminoma. MRI showing a smooth long TR hyperintensity in the pontine tegmentum, with axial FLAIR **A**; T1-weighted contrast enhancement of both oculomotor nerves **B**, coronal plane; C, axial plane). Repeated MRI showed the long TR hyperintensity in the pontine tegmentum more evident and extended **D**; persisting T1-weighted contrast enhancement of both oculomotor nerves (**E**, coronal plane; F, axial plane), with a slight reduction of left III cranial nerve swelling (red arrow) (colour figure online)

the patient developed sepsis from opportunistic infections, caused by Candida parapsilosis and Staphylococcus hominis. He was placed on intermittent non-invasive ventilation because of respiratory failure 24 h after percutaneous gastrostomy placement, and non-invasive ventilation was continued for several days. Clinical condition slowly improved, with slight improvement in oculomotor deficits and global limb weakness, and the patient was finally transferred for rehabilitation.

Case 3. A 72-year-old female, affected by HBV-related chronic hepatitis, arterial hypertension, and diabetes mellitus, had been suffering from fluctuant gait disturbance with unsteadiness and loss of balance, since the age of 60. The patient had history of bladder TCC, treated three time with surgery starting from fifteen years before, and in remission after 3-years follow-up. She was admitted to ND for progression of the gait ataxia, associated with speech disturbances, swallowing problems, urine and bowel incontinence. CT brain showed pontocerebellar atrophy with enlarged cisterna magna. We initially suspected spinocerebellar ataxia and started therapy with coenzyme Q10, suspended after two months due to lack of benefit. Next generation sequencing panel with copy number variation and repeat expansion analysis (Ataxia Comprehensive Panel) of genes associated with spinocerebellar ataxia excluded hereditary forms. CSF was negative for virology. She was suspected to be a case of SCD, hence paraneoplastic abs were sent which later came out to be positive for anti-**Yo** abs. MRI confirmed rapidly progressive cerebellar syndrome (online Fig. 2). Because of COVID-19 pandemic situation, the patient has not performed oncological follow-up to date, except for an unremarkable urinary tract ultrasound examination.

Case 4. A 47-year-old female presented multiple episodes of Generalized Tonic Clonic Seizures (GTCS) within five days. The patient had history of bilateral MAC, previously treated with surgery and hormonal therapy. After tumor recurrence was detected, she had refused further treatment for about a year. She was admitted to ND with status epilepticus with postictal stupor. She was given injectable Midazolam followed by Levetiracetam. Electroencephalography (EEG) revealed diffuse theta and delta waves, mixed with spikes. MRI brain showed long TR hyperintensities involving frontal and occipital lobes (Fig. 2). We started steroid therapy associated with acyclovir. Frequency and duration of seizures decreased. CSF was negative for virology. She was suspected to be a case of encephalitis probably

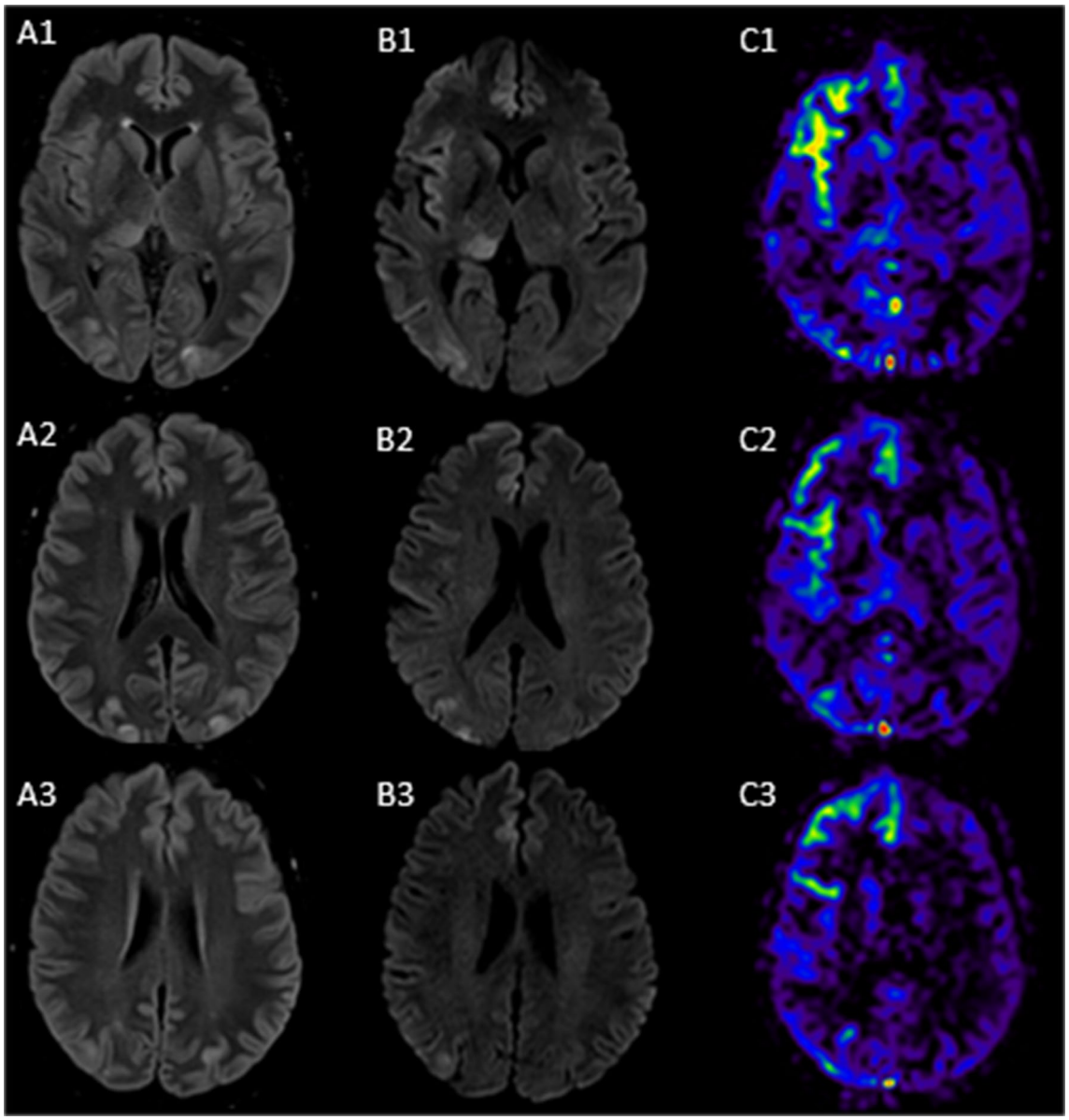

Fig. 2 Case 4. Extralimbic encephalitis associated with anti-CV2 abs and mammary adenocarcinoma relapse. MRI brain showing axial DWI (A1-A2-A3) and FLAIR (B1-B2-B3) hyperintense signal in frontal and occipital lobes, mainly in the right side. In addition, long-TR hyperintense sequences showed signal involving right basal ganglia and pulvinar (A1-B1). Hyperperfusion signal is evident in right frontal and occipital lobes on pcASL (C1-C2-C3) Fig. 3

autoimmune, and indeed serum and CSF were positive for anti-**CV2/CRMP** abs. WB-CT and PET revealed multiple hepatic and pulmonary metastasis. Repeated MRI showed decreased lobar involvement (online Fig. 3). The patient presented neurological improvement, despite residual weakness in both arms and paraplegia. Unfortunately, she refused further oncological follow-up.

Case 5. A 45-year-old male, with personal history of visceral leishmaniasis and orchiepidimitis, presented swallowing problems, speech disturbances, and progressive gait impairment. Neurological assessment in ND revealed dysphagia, mild dysarthria, and ataxic gait. Routine investigation including complete blood count, renal and liver function test, viral and tumor markers, urine microscopy was within normal limit. WB-CT and PET revealed hilomediastinal adenopathy. MRI showed brainstem, cerebellar, limbic and extralimbic involvement at different times (online Figs. 4–5). EEG showed sporadic diffuse beta activity within a background of alpha rhythm. CSF cytology showed normal cell count with normal protein and serum–CSF glucose ratio. Well-characterized anti-**Hu** abs were detected in CSF. IvMP (1 g/day) was given for 5 days

followed by oral prednisolone 1 mg/kg. He started showing dramatic improvement in speech and gait. Repeated brain MRI showed almost complete regression of long TR hyperintensities. After 18 months of follow-up, primary tumor has not been found to date.

Case 6. An 64-year-old woman, with no significant past or medical history, presented with subacute onset of limb numbness, mainly involving both legs, and gastrointestinal disorders (diarrhea, vomiting after meals, and marked weight loss), for six months. She was admitted to ND because of first episode of GTCS. Neurological assessment showed ataxic gait, and hypoesthesia in both legs and right arm. Routine investigation was normal except severe hyponatremia refractory to hypertonic saline. Brain CT and MRI revealed left hippocampal-amygdala involvement (Fig. 3A–D; online Fig. 6). WB-CT and PET revealed partly colliquated mediastinal mass. Paraneoplastic syndrome was suspected, including limbic encephalitis, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and predominantly axonal sensitive neuropathy. Sample for detection of paraneoplastic abs was sent, detecting both anti-**Hu** and anti-**SOX1** abs. FBS/EBUS was performed and high-grade PNT was detected (BCL-2 positive). The patient was transferred to oncology department for treatment, where chemotherapy was administered. Follow up MRI showed mesial temporal lobe atrophy (Fig. 3E-F).

Scenario 2 – Partially-characterized ONAs

Case 7. A 75-year-old female was admitted to Stroke Unit because of sudden onset of speech disturbance. She was a former smoker affected by toxic multinodular goiter, ulcerative colitis, arterial hypertension and atrial fibrillation, treated with direct oral anticoagulant. Neurological assessment showed slight right facial weakness and fluent aphasia (NIHSS 4). MRI showed DWI-FLAIR hyperintense signals in parietal and temporoinsular region on the left side (online Fig. 7). Hence, the diagnosis at presentation was cardioembolic stroke, but MRA did not reveal flow obstruction. On a more in-depth anamnestic questioning, the patient's relatives revealed that she has been suffering from behavior disturbances with agitation, hallucinations and cognitive decline since four years. In addition, two years earlier, the patient was treated with chemotherapy and radiotherapy because of anus BSCC. Routine blood chemistry was normal and viral markers were negative. EEG showed sharp slow waves in both hemispheres. CSF was normal. The search of ONAs revealed well-characterized anti-**SOX1** abs in CSF. IvMP

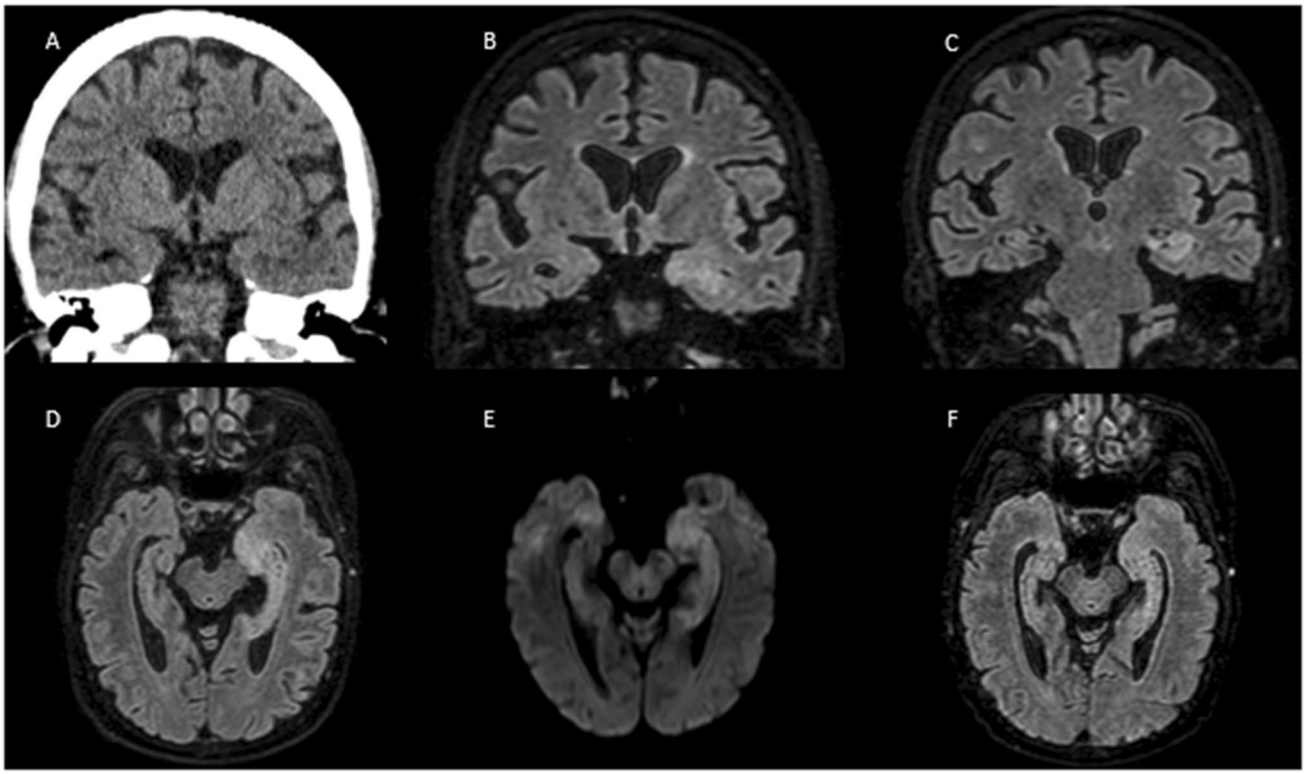

Fig. 3 Case 6. Limbic encephalitis associated with double onconeural antibodies positivity (anti-Hu and anti-SOX1) and lung neuroendocrine cancer. Brain CT revealed partial sulcal effacement of the left temporal lobe, adjacent to the temporal horn **A**. MRI brain showed FLAIR hyperintense signal in left hippocampal-amygdala formation **B**-**C**, coronal plane; **D**, axial plane). Follow up MRI revealed mesial temporal lobe atrophic regression on DWI **E** and FLAIR **F** axial planes

(1 g/day) was given for 5 days followed by oral prednisolone 1 mg/kg. She started showing mild improvement in sight and gait. Repeat brain MRI showed reduction of long TR hyperintensities. Unfortunately, after discharge we lost the patient to follow-up.

Case 8. A 67-year-old male had suffered from fluctuant symptoms for a month, consisting in bilateral eyelid ptosis, dysphagia, mild dysarthria, and hypophonia. The patient presented afterwards unsteady gait, and erectile dysfunction. ACHR negative myasthenia gravis was diagnosed using Single-Fiber Electromyography and Repetitive Nerve Stimulation, with evidence of nodular formation in the mediastinal CT chest. Thus, treatment with pyridostigmine, prednisone and azathioprine has been started, followed by resolution of ptosis and dysphagia. After few months, the patient was admitted to hospital for dyspnea due to massive pneumonitis. The patient was transferred to ND for the persistence of unsteady gait and dysarthria. MRI brain showed a cerebellar hyperhintense signal, with marked atrophy (online Fig. 8). The patient showed ataxic vermian and hemispheric syndrome with signs of impairment of I and II motor neuron, autonomic dysfunction and diffuse encephalopathy. He was positive for CSF anti-**Zic4 receptor** abs, associated with SCD. CECT thorax, abdomen and pelvis were done to screen for underlying malignancy. Advanced PLL was revealed, and repetitive hepatic lesions were detected, too. The patient was referred to oncology department, in order to start chemotherapy. However, after discharge the patient did not show for follow-up assessment.

Case 9. A 78-year-old female was admitted several times to ND because of progressive worsening of multidirectional nystagmus, gait impairment, and behavioral disturbances, for about two years. The patient had a history of several confusional episodes with vomit and diarrhea, followed by visual blurring, dizziness, and two tonic–clonic seizures associated with metabolic acidosis, treated with Levetiracetam. She was a former smoker affected by primary membranous nephropathy (aPLA2Rab), atherosclerotic stenoses of both carotid arteries with chronic cerebrovascular disease and subcortical atrophy, arterial hypertension, ischemic cardiomyopathy. Neurological assessment showed cognitive impairment with persecutory and jealousy delusional thinking, multidirectional saccadic eye movements (opsoclonus), involuntary muscle contractions (myoclonus), and truncal ataxia associated with akinesia, tremor, rigidity, hyperreflexia. MRI showed multiple lesions in the periventricular, subcortical, and infratentorial white matter (online Fig. 9), presumably related to chronic small vessel ischemic changes. Initial routine blood chemistry was normal, while tumor markers screening showed persistent positivity of serum CA19-9. EEGs obtained during opsoclonus, showed sharp slow waves in both hemispheres, without epileptiform activity. CSF was normal. The search of ONAs revealed partially characterized anti-**CASPR2** abs in CSF. IvMP (1 g/day) was given for 5 days followed by oral prednisolone 1 mg/kg. She started showing mild improvement in sight and gait. Repeated brain MRI showed stable long TR hyperintensities. WB-CT and PET performed after symptoms onset two years before were unremarkable, but repeated assessment revealed hilomediastinal adenopathy, associated with subpleuric "ground glass" parenchymal opacities in both lungs, and a parenchymal consolidation in the dorsal and basal region of left lung. Unfortunately, the patient developed a severe respiratory impairment, associated with an acute kidney impairment and electrolyte imbalances, leading to death before further investigation could be performed.

Case 10. A 63-year-old female had suffered from fluctuant symptoms for three months, consisting in dizziness and nausea, associated with progressive unsteadiness and loss of balance. The patient had a history of arterial hypertension, chronic cerebrovascular disease, primary biliary cirrhosis, and systemic lupus erythematosus with lupus nephritis. Chest CT scan revealed a mediastinal mass, but WB-CT and PET were unremarkable. Nevertheless, thymic and lymph node biopsies confirmed the diagnosis of unicentric hyaline vascular Castleman's disease. MRI brain showed a slight hyperhintense signal in the superior vermian cortex, associated with mild cerebellar and hippocampal atrophy (Fig. 4). Neurological assessment revealed limb plastic hypertonia and vermian ataxia, associated with rotational nystagmus, severe dysarthria, and dysdiadochokinesia in the upper limbs. She was positive for CSF anti **GAD65** abs, associated with cerebellar ataxia and stiff-person syndrome. The patient was treated with high dose IvIg therapy. Unfortunately, the patient developed sepsis from Serratia marcescens, but clinical condition slowly improved. After five days, the patient had a slight improvement in dizziness and limb hypertonia, and she was finally transferred for rehabilitation, starting treatment with prednisone (12.5 mg/die) and methotrexate (10 mg/week).

Scenario 3 – Negative ONAs

Case 11. An 80-year-old female, affected by diabetes mellitus and chronic lymphocytic leukaemia (CLL), presented progressive asthenia, fatigue, loss of appetite, severe weight loss within two months. After the onset of confusional state, she underwent MRI, which showed a right temporal lesion, suspected for intracerebral leukemic infiltration (online Fig. 10). However, hemato-oncological assessment excluded correlation between CLL and brain involvement. Thus, the patient was admitted to ND, showing mild soporous state (GCS 13). EEG showed background of diffuse, arrhythmic, and polymorphic theta-delta brain activity. Repeated MRI showed new long-TR

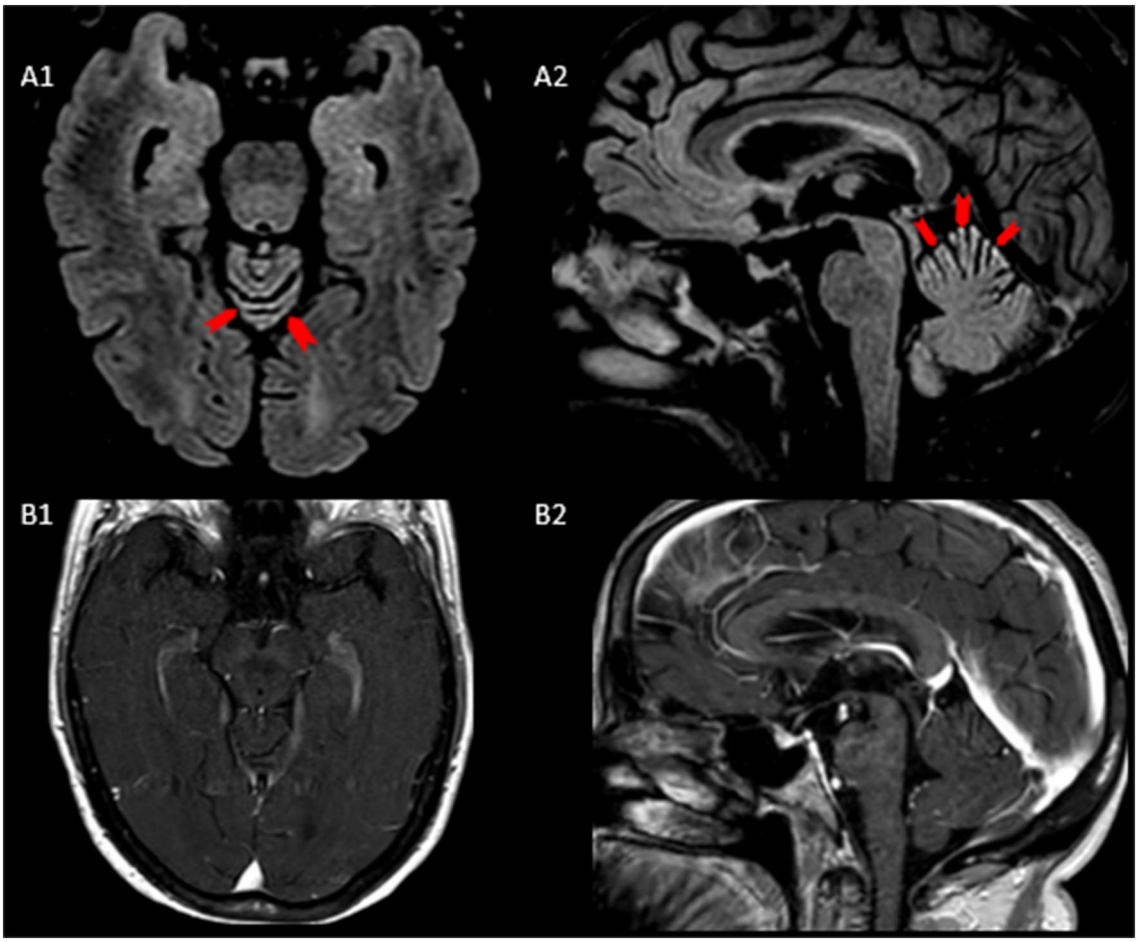

Fig. 4 Case 10. Stiff-person syndrome and cerebellar ataxia with anti-GAD65 abs and thymoma. MRI revealed FLAIR (A1, axial view; A2, sagittal view) slight hyperhintense signal in the superior vermian cortex (red arrowheads), associated with mild cerebellar and hippocampal atrophy. T1-weighted contrast-enhanced MRI (B1, axial view; B2, sagittal view) did not reveal contrast enhancement in the very same territory (colour figure online)

hyperintense signals involving several and bilateral cortical, subcortical, and infratentorial areas (online Fig. 11). CNS paraneoplastic involvement was suspected. CECT thorax, abdomen and pelvis were done to screen for underlying malignancy. Laboratory exams revealed refractory hyponatriemia, due to SIADH. CSF examination was normal and was negative for viruses. Sample for detection of paraneoplastic (Anti-Hu, Anti-Yo, Anti-Ri, Anti-Ma 1/2, Anti-CRMP-5 and Anti-amphiphysin) and VGKC abs was sent, which later came out to be **negative**. The patient was treated with pulse desametasone (8 mg/day) over seven days, and then IvMP (500 mg/day) over three days followed. Tolvaptan was administered for SIADH. Fluctuation of consciousness persisted after which she was given ibrutinib, with progressive but persistent improvement of symptoms. Unfortunately, the patient died few months later, because of CLL relapse.

Discussion

Laboratory findings and underlying malignancies

PNSs have an incidence of 0.25–3% in cancer patients presenting to tertiary care referral centers and a population-based incidence of 2–3 cases per million person-years [6]. In this study, we reported our single-center experience, and presented eleven illustrative cases (ten auto-abs positive, and one auto-abs negative) of PNSs involving CNS, with variable clinical spectrum and different radiological appearances. The laboratory findings in the present case series revealed that most patients received a clinical diagnosis with ONAs (10/11), whereas the most common PNSs (i.e. SCLC associated anti-Hu syndrome) were less frequently detected than expected from previous studies [6, 7]. This may reflect a referral bias in our community.

ONAs characterized in large and independent patient cohorts are called "well characterized", and comprises anti-Hu (or ANNA1), anti-Yo (PCA1), anti-Ma2, anti-Ri (ANNA2), anti-CV2/CRMP5, amphiphysin, and Tr/DNER (target antigen recently identified as being the Delta/Notch-like epidermal growth factor-related receptor, DNER) [1, 5]. These abs and corresponding antigens have been characterized by different laboratories and reported in large series of patients with PNSs. Their presence strongly favors the diagnosis of PNSs even if no tumor is found at initial evaluation. Furthermore, they can be very specific for some syndromes [1].

Concerning our case series, *well-characterized ONAs* had been detected in CSF of six patients.

The detection of these abs was crucial for the PNSs diagnosis among the patients presenting a CNS nonclassical syndrome. As a matter of fact, case 2 presented BE associated with anti-Ma2 abs, raising differential diagnostic concerns with neuromuscular junction disorders and cranial nerve variant of Guillain-Barré syndrome spectrum. Co-detection of Borrelia burgdorferi made diagnosis even more challenging, because a subset of patients with neuroborreliosis may develop a BE with a typical clinical course and distinct MRI findings [8]. Nevertheless, targeted antimicrobial therapy failed, since the patient's clinical conditions worsened, and PNS was suspected. Anti-Ma2 abs have well-described associations with testicular germ cell tumors, but seminomas have been described, too [1, 3, 9]. These patients might develop vertical gaze paresis that can sometimes progress to total external ophthalmoplegia [10]. Case 4 developed ELE associated with anti-CV2 abs and MAC relapse, as previously reported [3, 11]. Patients with anti CV2/CRMP5 abs more often develop chorea, uveitis, optic neuritis, and sensorimotor axonal neuropathy [1, 12]. Case 5 had anti-Hu associated BE [3, 11, 13], but screening for SCLC and testicular tumors has been negative to date. As above-mentioned, nonclassical PNS can be defined in presence of well-characterized ONAs, even without cancer detection [4]. If no tumor is detected at the time of PNS diagnosis, cancer surveillance should be done every 6 months for 4 years in PNS with ONAs [14]. Recently, Graus et al. [15] proposed three levels of diagnostic certainty (possible, probable, and definite PNS) based on a scoring system (PNS-Care Score) that considers the type of clinical phenotype, presence or absence of ONAs, and presence or absence of cancer. According to new proposed criteria, if no cancer was found after > 2 years, the diagnosis could be downgraded to possible.

Considering CNS classical syndromes, case 3 presented anti-Yo abs–mediated SCD. Anti-Yo is the antibody most frequently identified with the syndrome, especially in postmenopausal women, and it is associated with a very poor prognosis [15, 16]. The tumors more frequently involved are breast and ovarian cancer [3, 15]. Nevertheless, bladder TCC had been described also in patients presenting with SCD and anti-Yo abs response, whenever ovarian, adnexal, uterine, or breast cancer cannot be detected [17, 18]. Classical LE was the presentation of case 1 and 6. Case 1 had limbic and extra-limbic involvement associated with anti-Ma2 and NSCLC, according to previous findings [3, 11]. Anti-Ma2 abs manifestations include a syndrome that affects limbic structures (seizures, amnesia), the diencephalon (hyperphagia, hypersomnia, narcolepsy, cataplexy, endocrinopathy), and the upper brainstem (hypokinesis, rigidity, vertical gaze palsy) [1, 9]. Case 6, on the other hand, presented LE associated with double ONAs positivity (anti-Hu and anti-SOX1). The presence of anti-Hu had been described in previous studies in association with neuroendocrine tumors [3, 19]. SOX1 abs have been considered well-characterized ONAs in association with PNSs and SCLC, especially Lambert–Eaton myasthenic syndrome (LEMS) [2, 5]. They do not appear to have a strong association with a particular neurological phenotype, but seem to be cancer-specific serological biomarkers [20]. In a recent review, Sun et al [21] identified PNSs in 67.3% of the patients with anti-SOX1 abs and other coexisting ONAs, and in 21.2% of those with anti-SOX1 abs alone. Coexisting neuronal ONAs were not uncommon in patients with anti-SOX1 abs, being the association with anti-Hu the most frequent [21].

Actually, a classical LE was associated with anti-SOX1 abs alone in case 7. Apart from SCLC, anti-SOX1 could be detected in multiple cancers (prostate, penis, cecum, liver, and NSCLC) [22]. They could be associated with SCD, LE, and neuropathy, but, aside from LEMS, they are considered *partially characterized ONAs* [21]. In contrast to well-characterized ONAs, partially characterized abs are those for which there is limited clinical experience or the target antigen is unknown. Until better characterization occurs, they are of limited diagnostic value, although management of patients with these abs should be similar to those without paraneoplastic abs, including a comprehensive evaluation to rule out other possible causes [1]. Their detection increases the suspicion of underlying tumor, but diagnosis of a paraneoplastic syndrome should not be based solely on their finding [5]. Therefore, we could defined PNS only after the detection of a basal squamous carcinoma of anus in this patient. Concerning other classical CNS syndromes, case 8 had SCD with anti-Zic4 abs, which are partially-characterized ONAs mostly associated with SCLC [2, 5]. Nevertheless, they have been described also in Hodgkin and non-Hodgkin lymphomas [1]. In case 9, we described OMS associated with anti-CASPR2 abs and presumptive lung cancer, suspected after repeated WB-PET/CT examination. Paraneoplastic OMS have commonly revealed long-TR MRI hyperintensities in the pons and white matter [23, 24]. Adult cancers associated with OMS include SCLC with NSCLC and gynecologic tumors less frequently identified

[15]. CASPR2-IgG can manifest as Morvan's syndrome, peripheral nerve hyperexcitability, LE, cerebellar dysfunction, painful small-fiber neuropathies associated with neuropathic pain, or epilepsy [1, 5, 20]. CASPR2-IgG is associated with thymomas in about 20% of cases [1, 15], though other tumors have been reported rarely (melanomas, NSCLC, prostatic cancer, endometrial carcinoma, and pancreatic adenocarcinoma) [20, 25]. Recently, Rosenow et al. proposed a novel association between Caspr2 abs in a patient with mixed NSCLC-SCLC [23].

Nonclassical SPS and cerebellar ataxia were detected in case 10, associated with anti-GAD65 abs and thymoma. Paraneoplastic SPS is mostly associated with amphiphysin abs and breast cancer, while nonparaneoplastic SPS is usually associated with GAD65 abs [15, 26]. Nevertheless, some patients with anti–GAD65-associated SPS may have cancer, and actually multiple tumor types reported in individual patients (SCLC, breast, thymoma, neuroendocrine, lymphoproliferative disorders) [15, 17, 26]. Risk of underlying tumor is higher in males, increases with age, if presentation is a classic PNS, different from SPS or cerebellar ataxia, and association with ONAs against neuronal surface antigens (NSAbs), especially anti-GlyR abs associated with progressive encephalomyelitis with rigidity and myoclonus [1]. The response to treatment is variable, which might be explained by possible mixed T cell and abs-mediated pathogenic mechanisms [1]. Recently, Lee and Le described a new association between immune-mediated cerebellitis and Castleman's disease, a heterogeneous lymphoproliferative disorder of unknown etiology that can be associated with HIV, lymphoma, POEMS syndrome, paraneoplastic pemphigus and plasma cell dyscrasias [27, 28].

Finally, a classical LE was detected in absence of ONAs in CSF of case 11. Recent studies indicate that most LE cases previously considered 'seronegative' have NSAbs [29]. However, in world reference laboratories at least 7% of clinically definite LE are abs-negative to date [30]. For example, anti-NMDAR encephalitis, which is probably the most frequent form of NSAbs-associated encephalitis (NSAE), is often negative [31]. Abs-negative AE are mainly diagnosed after exclusion of other disorders, and therefore tend to have a poorer prognosis because of delayed treatments [32]. In addition, our patient was previously treated with Ibrutinib, which has been proven to penetrate the CNS at clinically effective levels by using a standard therapeutic oral dose. In the context of CNS paraneoplastic involvement, the suppression of ONAs secretion by neoplastic B-lymphocytes is a plausible mechanism of action [33].

Diagnostic sensitivity

CSF pleocytosis with early analysis (< 2 months) [34] should appear more sensitive than neuroimaging, where findings can be delayed [6]. In our case series, only two patients (case 4 and 11) performed an early analysis, but previous tumor directed therapy might have suppressed CSF pleocytosis or even ONA detection, as previously discussed. Only one case (case 2) presented CSF pleocytosis, despite the late analysis, raising the above-mentioned differential diagnosis problems.

MRI findings depend on time of analysis, with various abnormalities detected at different times, even in the same patient [6]. Specifically, long time of repetition (TR) sequences and T1-weighted contrast-enhanced MRI are mandatory in order to determine CNS involvement of PNSs [35]. In addition MRI perfusion studies may demonstrate marked abnormalities, showing increased cerebral blood flow in the affected area even before the detection on conventional MRI, which might present normal or slightly abnormal findings (see Fig. 2 and online Fig. 7) [36]. As a matter of fact, 3D pseudocontinuous arterial spin labeling (pcASL) may be useful in demonstrating perfusion reduction after therapy (online Fig. 3) [36].

Treatment outcomes and survival

Treatment of PNSs should be closely coordinated with an experienced care team, including an oncologist, neurologist, and surgeon if necessary [3]. Empiric treatment algorithms elaborated in published opinions and consensus guidelines should be followed, meanwhile therapeutic guidelines from prospective clinical trials are lacking [15, 37]. Successful treatment of PNSs with ONAs directed to cell surface membrane antigens has been reported following the use of steroids, PlEx, IvIg, and corticosteroid-sparing immunosuppressive agents, with marked patient improvement [38, 39]. Nevertheless, uniformity of treatment is lacking, even within the given series, and it is still unclear what might be the actual effect of these treatments on lymphocyte-mediated pathophysiology in PNSs [17]. In addition, timing is another critical point for treatment outcome, whereas most series reported that immunotherapy was started after weeks or months from symptom onset [17, 40]. Concerning PNSs with ONAs direct to intracellular neuronal antigens, such as anti-Yo or anti-Hu, neurological deficits result from immune-mediated neuronal death, and clinical symptoms manifest as neuronal reserve is exhausted [17]. As a result, these cases do not significantly improve, and therefore time is of the utmost importance in initiating treatment [6, 17].

In our case series, only two patients (case 2 and 6) had a poor response to immunotherapy. In case 2, it mainly depended on intercurrent opportunistic infection (see Clinical scenario in supplemental text). As mentioned before, the response to treatment in patients harboring anti-Hu and anti-Yo ONAs is greatly disappointing [6], and therefore it comes as no surprise the lack of improvement both in case

6 (with double ONAs positivity) and in case 3 (untreated). Nevertheless, with an early PNS diagnosis, these patients may have a long-term survival and benefit from a more favorable outcome, because of the limited stage cancer and the immunologic response to the onconeural antigen, which may have an anti-tumor effect [6, 41]. Considering the overall survival, two patients died at the end of follow-up (case 9 and 11), because of systemic complication leading to death (see Clinical scenario in supplemental text). Specifically, about seronegative PNSs as in case 11, prospective studies are required in order to determine whether timely treatments can improve prognosis and which therapeutic strategy should be used [30].

Finally, we could perform definitive diagnosis of PNS only after several months in the majority of cases, supporting the importance of the immunomodulatory therapy before the investigations were completed.

Limitations

The study is based on a single center experience, which makes it difficult to avoid possible biases. There are several limitations in the current investigation. First, the very small number of patients and the retrospective design of the investigation are clear limitations. Secondly, since 19.2% of the original cases were excluded because of incomplete information, our nosographic picture of PNSs involving CNS may be biased. Thirdly, approximately two-thirds of the patients underwent neuronal Ab screening with commercial diagnostics only, with possible exclusion of some patients with non-classical syndrome. The institutional laboratory methods could detect only ONAs directed against intracellular-neuronal antigens, whereas we sent samples to different laboratories for them to test ONAs directed against neuronal receptors or other cell membrane antigens. Therefore, some small interlaboratory bias might have occurred. Fourthly, the response to immunosuppressive treatments was judged a posteriori according to each treating physician's opinions. We could not achieve the uniformity of treatment within this case series, according to the previous studies, because of the lack of guidelines from prospective clinical trials, as previously discussed.

Conclusion

Our study offers a practical approach with real-world clinical examples of PNSs involving CNS, also underlying common misdiagnosis or diagnostic delays related to differential diagnosis, since the decision-making process may be challenging in the acute care setting. Hence, we support the utmost importance of early recognition of PNSs involving CNS in order to prevent unfavorable outcome, such as devastating neurologic disability or death. Actually, PNSs can be readily detected through the recognition of the clinical syndrome and modern diagnostic techniques. Experienced laboratories are fundamental to the most accurate auto-abs diagnostics [42]. Screening for occult malignancies should not be limited to patients with classical CNS syndrome, because a prompt treatment of the underlying malignancy is extremely important in the overall patient outcome. Late presentations should not discourage initiation of treatment, even over the period of follow-up, whenever the disease presents a relapsing course. Empiric immunomodulatory therapy may have to be considered before the medical evaluation is completed, because of the high PNS-associated neurological morbidity and mortality.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The paper does not report on primary research. All data analyzed were collected as part of routine diagnosis and treatment.

Informed consent Informed consent requirement was waived by the Institutional Review Board (minimal risk). All data analyzed were collected as part of routine diagnosis and treatment.

References

1. Grativvol RS, Cavalcante WCP, Castro LHM, Nitrini R, Simabukuro MM (2018) Updates in the diagnosis and treatment of

paraneoplastic neurologic syndromes. Curr Oncol Rep. https://doi.org/10.1007/s11912-018-0721-y
2. Zoccarato M et al (2017) Diagnostics of paraneoplastic neurological syndromes. Neurol Sci 38:237–242
3. Galli J, Greenlee J (2020) Paraneoplastic diseases of the central nervous system. F1000Research 9:167
4. Graus F et al (2004) Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 75:1135–1140
5. Leypoldt F, Wandinger KP (2014) Paraneoplastic neurological syndromes. Clin Exp Immunol 175:336–348
6. Chan AM, Baehring JM (2019) Paraneoplastic neurological syndromes: a single institution 10-year case series. J Neurooncol 141:431–439
7. Giometto B et al (2010) Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 67:330–335
8. Pfefferkorn T, Röther J, Eckert B, Janssen H (2021) Brainstem encephalitis in neuroborreliosis: typical clinical course and distinct MRI findings. J Neurol 268:502–505
9. Dalmau J et al (2004) Clinical analysis of anti-Ma2-associated encephalitis. Brain 127:1831–1844
10. Honnorat J, Joubert B (2018) Movement disorders in autoimmune encephalitis and paraneoplastic neurological syndromes. Rev Neurol (Paris) 174:597–607
11. Titulaer MJ et al (2011) Screening for tumours in paraneoplastic syndromes: Report of an EFNS task force. Eur J Neurol 18:19-e3
12. Honnorat J et al (2009) Onco-neural antibodies and tumour type determine survival and neurological symptoms in paraneoplastic neurological syndromes with Hu or CV2/CRMP5 antibodies. J Neurol Neurosurg Psychiatry 80:412–416
13. Saiz A et al (2009) Anti-Hu-associated brainstem encephalitis. J Neurol Neurosurg Psychiatry 80:404–407
14. Rössling R, Prüss H (2020) SOP: antibody-associated autoimmune encephalitis. Neurol Res Pract. 7:1–7
15 Graus F et al (2021) Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurol Neuroimmunol. neuroinflammation 8:e1014
16. Le May M, Dent S (2018) Anti-Yo antibody–mediated paraneoplastic cerebellar degeneration associated with cognitive affective syndrome in a patient with breast cancer: a case report and literature review. Curr Oncol 25:e585
17. Greenlee JE et al (2022) Paraneoplastic and other autoimmune encephalitides: antineuronal antibodies, T lymphocytes, and questions of pathogenesis. Front Neurol 12:2131
18. Greenlee J et al (1999) Association of anti-Yo (type I) antibody with paraneoplastic cerebellar degeneration in the setting of transitional cell carcinoma of the bladder: detection of Yo antigen in tumor tissue and fall in antibody titers following tumor removal. Ann Neurol 45:805–809
19. Lee SK, Lee S (2016) The laboratory diagnosis of autoimmune encephalitis. J Epilepsy Res 5:45–52
20. Devine MF, Kothapalli N, Elkhooly M, Dubey D (2021) Paraneoplastic neurological syndromes: clinical presentations and management. Ther Adv Neurol Disord 14:1–19
21. Sun X et al (2020) Anti-sox1 antibodies in paraneoplastic neurological syndrome. J Clin Neurol 16:530–546
22. Berger B et al (2016) Prevalence of anti-SOX1 reactivity in various neurological disorders. J Neurol Sci 369:342–346
23. Rosenow CS et al (2022) case report: opsoclonus-myoclonus syndrome associated with contactin-associated protein-like 2 and acetylcholine receptor autoantibodies in the setting of non-small cell lung carcinoma. Neurohospitalist 12:100–104
24. Tsutada T, Izumi T, Murakami T (1996) Correlation of clinical improvement with pontine lesions in opsoclonus-myoclonus syndrome. Osaka City Med J 42:53–60
25. Boyko M, Au KLK, Casault C, de Robles P, Pfeffer G (2020) Systematic review of the clinical spectrum of CASPR2 antibody syndrome. J Neurol 267:1137–1146
26. Saiz A et al (2008) Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: Diagnostic clues for this association. Brain 131:2553–2563
27. Lee S, Le S (2015) A new association between castleman disease and immune-mediated cerebellitis. JAMA Neurol 72:722–723
28. Bonekamp D, Horton KM, Hruban RH, Fishman EK (2011) Castleman disease: the great mimic. Radiographics 31:1793–1807
29. Graus F, Dalmau J (2012) Paraneoplastic neurological syndromes. Curr Opin Neurol 25:795–801
30. Graus F et al (2018) Syndrome and outcome of antibody-negative limbic encephalitis. Eur J Neurol 25:1011–1016
31. Zuliani L, Zoccarato M (2020) Open issues in antibody-mediated encephalitis. Future Neurol 15:2–5
32. Gastaldi M et al (2020) Subgroup comparison according to clinical phenotype and serostatus in autoimmune encephalitis: a multicenter retrospective study. Eur J Neurol 27:633–643
33. Ferrer A et al (2008) Central nervous system involvement in mantle cell lymphoma. Ann Oncol 19:135–141
34. Giometto B et al (2010) Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 67:330–335
35. Madhavan AA et al (2020) Imaging review of paraneoplastic neurologic syndromes. AJNR Am J Neuroradiol 41:2176
36. Li R et al (2022) Brain perfusion alterations on 3D pseudocontinuous arterial spin-labeling MR imaging in patients with autoimmune encephalitis: a case series and literature review. AJNR Am J Neuroradiol 43:701–706
37. Graus F et al (2016) A clinical approach to diagnosis of autoimmune encephalitis. Supplementary webappendix Lancet Neurol 15:391–404
38. Abboud H et al (2021) Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management. J Neurol Neurosurg Psychiatry 92:897–907
39. Abboud H et al (2021) Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry 92:757–768
40. Vernino S, O'Neill BP, Marks RS, O'Fallon JR, Kimmel DW (2004) Immunomodulatory treatment trial for paraneoplastic neurological disorders. Neuro Oncol 6:55–62
41 Sadeghian H, Vernino S (2009) Progress in the management of paraneoplastic neurological disorders. Ther Adv Neurol Disord. https://doi.org/10.1177/1756285609349521
42. Graus F et al (2016) A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 15:391–404