JCN Open Access REVIEW

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2020;16(4):530-546 / https://doi.org/10.3988/jcn.2020.16.4.530

Anti-SOX1 Antibodies in Paraneoplastic Neurological Syndrome

Xuan Sun[a*]
Jiping Tan[a*]
Hui Sun[b]
Yan Liu[a]
Weiping Guan[a]
Jianjun Jia[a]
Zhenfu Wang[a]

[a]Geriatric Neurological Department of the Second Medical Centre, National Clinical Research Center of Geriatric Diseases, Chinese PLA General Hospital, Beijing, China
[b]Department of Neurology, the First Medical Centre, Chinese PLA General Hospital, Beijing, China

Anti-Sry-like high mobility group box (SOX) 1 antibodies (abs) are partly characterized onconeural autoantibodies (autoabs) due to their correlation with neoplastic diseases. Anti-SOX1 abs are associated with various clinical manifestations, including Lambert-Eaton myasthenic syndrome (LEMS) and paraneoplastic cerebellar degeneration (PCD). However, the clinical characteristics of patients with anti-SOX1 abs have not been described in detail. This review systematically explores the reported patients with anti-SOX1 abs and analyzes these cases for demographic characteristics, clinical features, coexisting neuronal autoabs, neuroimaging findings, treatment, and clinical outcomes. In addition, considering that PCD is the most common paraneoplastic neurological syndrome and that the association between PCD and anti-SOX1 abs remains unclear, we focus on the presence of autoabs in relation to PCD and associated tumors. PCD-associated autoabs include various intracellular autoabs (e.g., anti-Hu, anti-Yo, anti-Ri, and anti-SOX1) and cell-surface autoabs (anti-P/Q-type voltage-gated calcium channel). Commonly involved tumors in PCD are small-cell lung cancer (SCLC), gynecological, and breast tumors. LEMS is the most common clinical symptom in patients with anti-SOX1 abs, followed by PCD, and multiple neuronal autoabs coexist in 47.1% of these patients. SCLC is still the predominant tumor in patients with anti-SOX1 abs, while non-SCLC is uncommon. No consistent imaging feature is found in patients with anti-SOX1 abs, and there is no consensus on either the therapy choice or therapeutic efficacy. In conclusion, the presence of anti-SOX1 abs alone is a potential predictor of an uncommon paraneoplastic neurological disorder, usually occurring in the setting of LEMS, PCD, and SCLC. The detection of anti-SOX1 abs contributes to an early diagnosis of underlying tumors, given the diversity of clinical symptoms and the absence of characteristic neuroimaging features.

Key Words SOXB1 transcription factors, antibodies, paraneoplastic cerebellar degeneration, small cell lung carcinoma, carcinoma, non-small-cell lung.

INTRODUCTION

Paraneoplastic neurological syndrome (PNS) is a rare immune-mediated consequence of an immune cross response between a tumor and the nervous system, which may be diagnosed based on the presence of specific onconeural antibodies (abs).[1] Fewer than 1% of cancer patients overall develop PNS,[2] but it is important to distinguish PNS in a timely manner because this can allow occult tumors to be identified.

PNS comprises a heterogeneous group of disorders that can affect every part of the nervous system, involving the central nervous system, peripheral nervous system, and neuromuscular junction.[3] Classic PNS includes neurological syndromes that are often associated with cancer, such as paraneoplastic cerebellar degeneration (PCD), Lambert-Eaton myasthenic syndrome (LEMS), encephalomyelitis, paraneoplastic limbic encephalitis (PLE), and sensory neuronopathy.[3] PCD is the most common PNS and originates from autoimmune

Received January 8, 2020
Revised May 6, 2020
Accepted May 6, 2020

Correspondence
Zhenfu Wang, MD, PhD
Geriatric Neurological Department of the Second Medical Centre, Chinese PLA General Hospital, 28 Fuxing Road, Haidian Distrct, Beijing 100853, China
Tel +86-010-66876367
Fax +86-010-66876367
E-mail zhenfuw@sina.com

*These authors contributed equally to this work.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

 Copyright © 2020 Korean Neurological Association

damage to the cerebellum.[4] Classic PCD has a subacute course, with less than 12 weeks of a severe cerebellar syndrome with no evidence of cerebellar atrophy other than that expected based on the age of the patient with a Rankin Scale score of at least 3 (indicating that symptoms significantly interfere with the lifestyle or prevent a totally independent existence).[3] PCD patients exhibit various cerebellar ataxia symptoms such as ataxia, dysmetria, dysarthria, nystagmus, dizziness, and vertigo. Although studies have investigated the association between PNS autoabs and PCD, the neuronal autoantibodies (autoabs) in PCD have not been fully described.[2]

Two types of PNS autoabs are classified based on the target antigen location: intracellular (onconeuronal) targets and cell-surface targets.[5] In recent decades, the detection of well-characterized onconeuronal autoabs [e.g., anti-Hu, anti-Yo, anti-collapsin response-mediator protein-5 (CRMP5), and anti-amphiphysin] has improved the ability to diagnose PNS. These autoabs react with antigens expressed in both tumor and neuronal structures, which prompted the hypothesis of autoimmune pathogenesis.[5] In the past 15 years, anti-glial nuclear ab (AGNA) targeting the Bergmann glia cells of the adult cerebellum was believed to be an intracellular ab associated with PNS.[6] Proteins of Sry-like high mobility group box (SOX) 1 were identified as the corresponding antigens generating the immune response.[7] SOX1 proteins are developmental transcription factors that share a conserved DNA-binding protein and play a vital role in central nervous system development.[8-10] Anti-SOX1 abs have been associated with various neurological syndromes in which LEMS is thought to be the most frequent clinical characteristic.[11] Aside from LEMS, PCD, PLE, and neuropathy have also been reported.[12] However, the prevalence rates of these clinical symptoms and other clinical features in patients with anti-SOX1 abs still need to be systematically elucidated.

While the specific pathogenesis remains unclear, anti-SOX1 abs are believed to be malignant neoplasm-related onconeural autoabs due to their close relationship with tumors. Small-cell lung cancer (SCLC) is the most prominently associated tumor in PNS, reportedly being present in up to 3−5% of PNS cases.[4,13] Similarly, anti-SOX1 abs are also considered serological markers of SCLC,[12,14,15] and they appear in up to 36.5% of patients with SCLC.[15] Additionally, anti-SOX1 abs have reportedly been the most frequently detected autoabs in 49% of patients with PCD and SCLC.[16] However, the understanding of the underlying mechanism of non-SCLC (NSCLC)-associated PNS is hindered by the rarity of the cases, with only a few studies described NSCLC patients presenting with anti-SOX1 abs.[12,17-21]

Since PCD is considered the most common PNS, we reviewed the neuronal autoabs and associated tumors presenting as PCD (Table 1). In addition, we critically reviewed the clinical features of 486 cases of anti-SOX1 abs with identified tumors in 32 English-language and 4 Chinese-language studies reported up to December 2019 (Tables 2 and 3). The purpose of this study was to obtain a comprehensive understanding of the clinical characteristics of anti-SOX1-abs-positive patients, and to better recognize neuronal autoabs in PCD and their associated tumors.

NEURONAL ABS IN PCD AND THEIR ASSOCIATED TUMORS

Immune-mediated cerebellar ataxias (IMCAs) represent a clinical entity comprising various autoimmune-based etiologies such as PCD, gluten ataxia, anti-glutamate decarboxylase 65 (GAD65) ab-associated cerebellar ataxia, postinfectious cerebellitis, and opsoclonus myoclonus syndrome.[22] PCD is a kind of IMCA that is characterized by immune-mediated neuronal dysfunction resulting in selective damage to the cerebellar Purkinje cells triggered by a neoplasm.[23] PCD is defined as cerebellar ataxia with the development of cancer within 5 years or the appearance of neuronal autoabs that ensure a definite diagnosis of PCD.[1] Cerebellar ataxia is the first manifestation of neoplasms in 70% of PCD patients.[1]

Neuronal abs

Immune responses are increasingly being associated with PCD (Table 1). Some are directly correlated with cerebellar symptoms, whereas others lack syndrome specificity and might simply indicate a tumor-induced immune response. The relevant autoabs have included well-characterized intracellular (nuclear or cytoplasmic) autoabs such as Hu, Yo, Ri, CV2/CRMP5, and Ma2 autoabs; partly characterized intracellular autoabs such as SOX1 and zinc-finger protein (Zic) 4 autoabs; and cell-surface (synaptic or plasma membrane) autoabs such as voltage-gated calcium channel (VGCC) (P/Q type), Tr, and mGluR1 autoabs (Table 1). Among them, anti-Yo autoabs are the most common.[22,24]

Studies performed over the past 15 years have revealed the presence of PCD in patients with anti-SOX1 abs,[21,25] and we also found chronic PCD with anti-SOX1 abs in patients with NSCLC of mediastinal squamous-cell carcinoma. Although the precise mechanisms underlying PCD in anti-SOX1 abs remain unclear, they are attributed to the SOX1 antigen and related proteins that have accumulated in the Purkinje cell layer of the adult human cerebellum.[26,27]

Associated tumors

PCD generally predates a cancer diagnosis. Cerebellar ataxia occurs before the tumor has been detected in nearly 30%

Table 1. Neural autoantibodies in PCD and their associated tumors

Ab	PCD and additional neurological symptoms of ab	Oncological association of ab with PCD
Intracellular ab		
Anti-SOX1	LEMS,[7,11] PCD,[16,25] sensory or sensorimotor polyneuropathy,[46] PLE[12,17,55,65]	SCLC,[7,11,12,16,40,44,55] NSCLC (squamous-cell lung cancer) (Sun et al.)
Anti-Yo	PCD, brainstem encephalitis[24]	Breast and gynecological (uterus, ovary, fallopian tube) cancer,[3,24,29,30,77,78] SCLC,[15,30] NSCLC,[30,31] digestive system cancer,[79-81] prostate cancer,[82] pleural cancer[83]
Anti-Hu	LEMS, PCD,[16] PLE, paraneoplastic encephalomyelitis, myelitis, neuronopathy, autonomic dysfunction,[1,3] opsoclonus myoclonus syndrome[24]	SCLC,[15,24,29,84] NSCLC,[30] prostate cancer,[85] head and neck cancer (spindle cell carcinoma),[32] intestinal cancer[86]
Anti-CV2/CRMP5	PCD,[87] paraneoplastic encephalomyelitis, chorea, uveitis, optic neuritis, peripheral neuropathy,[1] chronic gastrointestinal pseudo-obstruction, optical neuropathy[3]	SCLC,[29,88] NSCLC,[30] thymoma,[88] prostate cancer[89]
Anti-Ri	PCD,[24] opsoclonus myoclonus syndrome, brainstem encephalitis, PLE, myelitis,[24] neuropathy[68]	Breast and gynecological cancer,[24,30,90,91] SCLC[1,92]
Anti-Ma2	Paraneoplastic encephalomyelitis, PLE, brainstem encephalitis, PCD[3]	NSCLC,[1,93] testis cancer[3]
Anti-Zic4	PCD	SCLC[1,94,95]
Cell-surface ab		
Anti-VGCC$_{P/Q}$	LEMS,[75] PCD[33]	SCLC,[33] NSCLC,[33,34] MCC[96,97]
Anti-Tr	PCD,[24] PLE[24]	Hodgkin's lymphoma,[1,2,16,24,29,30] NSCLC (squamous cell lung carcinoma)[35]
Anti-mGluR1	PCD,[24] PLE,[24] LEMS[3]	Hodgkin's lymphoma,[1,24,98] prostate adenocarcinoma[2]
NSCLC without ab detected	PCD	2 patients with squamous-cell lung cancer,[38,39] 16 NSCLC patients without identified tissue type[30,36,37]

Ab: antibody, CRMP5: collapsin response-mediator protein-5, LEMS: Lambert-Eaton myasthenic syndrome, MCC: Merkel cell carcinoma, NSCLC: non-SCLC, PCD: paraneoplastic cerebellar degeneration, PLE: paraneoplastic limbic encephalitis, SCLC: small-cell lung cancer, SOX: Sry-like high mobility group box, VGCC: voltage-gated calcium channel, Zic: zinc-finger protein.

of patients.[28] Tumors that are more commonly involved in PCD are lung tumors (anti-Hu, anti-CV2/CRMP5, anti-VGCC, and anti-SOX1), gynecological, and breast tumors (anti-Yo and anti-Ri) and, less frequently, Hodgkin's lymphoma (anti-Tr and anti-mGluR1) (Table 1).[2,24,29] The most commonly associated type of lung cancer is SCLC, which is highly immunogenic.[4] SCLC is a neuroendocrine differentiated tumor, and SCLC tumor cells contain various neuronal antigens present in the nervous system; therefore, SCLC is frequently involved in PNS.

On the other hand, PCD is less common in NSCLC than in SCLC.[13,30] Evidence of PCD associated with NSCLC comes from only a few case reports and relevant neuronal autoabs, including those to SOX1, Yo, Hu, CV2/CRMP5, Ma2, VGCC, and Tr.[1,30-35] Furthermore, 18 reported patients with NSCLC presented PCD without identifiable autoabs.[30,36-39] In four patients with NSCLC, squamous-cell lung carcinoma was demonstrated with anti-Tr abs in one patient, anti-SOX1 abs in one patient, and no identified autoabs in the other two patients (Table 1).[35,38,39]

ANTI-SOX1 ABS

Demographic characteristics

This systematic review of 520 cases of patients with anti-SOX1 abs included 34 cases without an identified cancer. Among 284 patients with anti-SOX1 abs in which the sex was reported, more males (*n*=194, 68.3%) than females (*n*=90, 31.7%) have been described, with an age range from 17 years to 87 years (Table 2).

Neurological disorder

PNS was identified in 67.3% (*n*=350) of the patients with anti-SOX1 abs and other coexisting autoabs, and in 21.2% (*n*=110) of those with anti-SOX1 abs alone. Since the presence of coexisting autoabs may also result in the development of clinical symptoms, and hence make it difficult to identify the symptoms attributable specifically to anti-SOX1 abs, we analyzed only clinical manifestations in the patients with anti-SOX1 abs alone (Table 3).

The neurological presentations of patients with anti-SOX1 abs are more diverse than traditionally recognized, and they can be misdiagnosed as neurodegenerative disorders. The neurological dysfunction associated with anti-SOX1 abs may involve multiple levels of the neuraxis, including the limbic system, cerebellum, peripheral nervous system, and neuromuscular junction. Among the 110 anti-SOX1-abs-positive patients with identified cancer, LEMS (30.0%, *n*=33) was the most common PNS,[6,11,12,40-43] followed by PCD (18.2%, *n*=20),[12,16,25,40,44] PLE (18.2%, *n*=20),[6,12,17,40,45] and neuropathy (8.2%, *n*=9) (Table 3).[6,41-43,46]

As the most frequent symptom in patients with anti-SOX1 abs, 30.0% of the patients in our review had LEMS and anti-SOX1 abs alone. In the literature there are reports of 64% of patients with both LEMS and SCLC presenting with anti-SOX1 abs,[7] compared with 22−36.5% of patients with SCLC alone.[7,11,15,47] We presume that there were still some patients with LEMS and SCLC among the 30.9% of anti-SOX1 abs patients with unidentified PNS, based on most of them having SCLC.[12,48] Therefore, the actual proportion of patients with LEMS and anti-SOX1 abs should exceed 30.0%. Our review data support the notion that anti-SOX1 abs could be the main predictor of SCLC in patients with LEMS.[49]

It was intriguing that 78 patients with anti-SOX1 abs alone showed no clinical manifestations of PNS. Antineuronal autoabs were believed to be immune effectors of neurological dysfunction with regards to membranous antigens (i.e., calcium-channel abs). However, anti-SOX1 abs are directed against intracellular nuclear proteins, which are subject to a cytotoxic T-cell response.[5,50] Therefore, anti-SOX1 abs that per se exert a direct pathogenic effect in PNS are unlikely. This is also supported by the absence of clinical symptoms or survival divergence between anti-SOX1-abs-positive and anti-SOX1-abs-negative patients in SCLC. Nevertheless, similar to other onconeural autoabs (e.g., anti-Hu and anti-Yo), anti-SOX1 abs are still useful for reminding physicians to treat underlying tumors in patients.

Coexisting tumors

Cancers were identified in 93.5% (*n*=486) of the 520 patients with anti-SOX1 abs. The presence of anti-SOX1 abs is a potential predictor of underlying SCLC, and SCLC represented the predominant cancer (85.2%, 414 of the 486 cancer patients) (Table 3).[6,7,11,12,15,16,21,40-49,51-61] The underlying pathogenic mechanism may be due to the immunoreactivity of SCLC patients against epitopes of the conserved high-mobility group box;[14] apart from preventing neural differentiation in progenitor cells and being mainly expressed in the developing nervous system and down-regulated in adults, SOX1 proteins also affect the airway epithelial differentiation and are highly immunogenic.[14,18]

Until now, little has been known about the prevalence and underlying pathogenesis of NSCLC and anti-SOX1-abs-related PNS. Our study found that only 22 patients with anti-SOX1 abs had NSCLC corresponding to other histological types, which were described as squamous-cell cancer (*n*=6),[17,19] adenocarcinoma (*n*=7),[19,21] bronchial carcinoid (*n*=1),[46] polymorphic NSCLC (*n*=1),[21] and unspecified NSCLC (*n*=7) (Table 3).[6,12,20] We found that anti-SOX1 abs in patients with NSCLC of mediastinal squamous-cell carcinoma con-

Table 2. Anti-SOX1-abs-related clinical characteristics

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Anti-SOX1 abs alone										
Case reports and series										
Case (Sun et al.)	PCD	NSCLC (1) (middle mediastinal tumor of poorly differentiated squamous-cell cancer	79/M	Positive	NA	Chronic	None	Chemotherapy and radiotherapy	None	29 months to December 2019: mild-to-moderate ataxia involving limbs, and walking assisted
Li et al.[40]	LEMS, PLE, PCD	SCLC (1) (mediastinal lymph nodes)	61/M	Positive	NA	Chronic	Brain MRI normal. Spinal MRI showed enhancement of the thorax in front of 5–6 centrum, T6 and T12 destructive vertebral body lesions	Chemotherapy and radiotherapy	None	Neurological symptoms did not improve significantly. Patient died 15 months after diagnosis
Alessandro et al.[25]	PCD, photophobia	No underlying cancer during 3-year follow-up	63/M	Positive	Negative	PCA (chronic), photophobia (subacute)	Diffuse hyperintensities in cerebellum and brainstem without enhancement	None	IV methylprednisolone with subsequent oral prednisone (40 mg) for 2 years	At 3 years, progressing to severe incapacitating ataxia, confined to wheelchair, and marked photophobia
Ji et al.[44]	PCD	SCLC (1)	53/M	Positive	NA	Subacute	None	Local excision and chemotherapy	IVIg	At 3 months, no improvement in PCD
Mirallas et al.[41]	LEMS, neuropathy	SCLC (1)	66/M	Positive	NA	Chronic	NA	Chemotherapy	None	At 15 months, improvement of gait instability, but slight paresthesia of both lower limbs remained
Cho et al.[17]	PLE presenting as new-onset refractory status epilepticus	NSCLC (1) (squamous-cell lung cancer)	76/M	Positive	NA	Acute	None	Chemotherapy and radiotherapy	IVIg	Full recovery within 15 days
Ge et al.[42]	LEMS, neuropathy (2)	SCLC (1) Esophagus cancer (1)	45/M 61/M	Positive	NA	Acute Chronic	None	Chemotherapy for NSCLC patients	IVIg for NSCLC patient	NSCLC patient did not respond to chemotherapy and IVIg therapy. SCLC patient abandoned therapy

Table 2. Anti-SOX1-abs-related clinical characteristics (continued)

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Liu et al.[43]	LEMS, neuropathy	SCLC (1)	72/M	Positive	NA	Subacute	None	None	None	Patient abandoned therapy and died 5 months after disease onset
Research articles										
Graus et al.[6¶]	LEMS (13), neuropathy (3), PLE (2), no PNS (13) for 31 SCLC patient. PNS of 3 NSCLC patients was NA	SCLC (31) NSCLC (3)	NA	Positive	4 positive, 1 negative	NA	NA	NA	NA	NA
Ruiz-García et al.[12]	PCD (15), PLE (15), LEMS (14), other PNS (20), no PNS (7)	SCLC (64/71) NSCLC (3/71) Other (breast, prostate) (2/71)	63 (median), 22–87 (range), 55×M, 16×F	Positive	NA	NA	NA	NA	NA	NA
Berger et al.[18]	PNS (4) No PNS (1)	Thyroid cancer (1/5), Hodgkin's lymphoma (1/5), breast cancer (2/5), multiple cancers of the prostate, penis, cecum, and liver, and NSCLC (1/5)	29–73 (range), 2×M, 3×F	Positive	NA	NA	NA	NA	NA	Follow-up time ranged from 1 to 11 years (longest in patient with thyroid cancer)
Sabater et al.[16]	PCD (1)	SCLC (1)	NA	Positive	NA	NA	NA	NA	NA	NA
Graus et al.[45†]	PLE (1)	SCLC (1)	81/F	Positive	NA	NA	Bilateral temporal Lesions	Chemotherapy	Steroids	No response to treatment and had died at 30-month follow-up
Li and Li[19]	NA	10 NSCLC patients: squamous-cell carcinoma (4), adenocarcinoma (6)	NA	Abs identified by immunohistochemistry in biopsy specimens		NA	NA	NA	NA	NA

Table 2. Anti-SOX1-abs-related clinical characteristics (continued)

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Titulaer et al.[11]	LEMS (1) No PNS (26)	SCLC (27)	32–78 (range)*, 49×M, 23×F*	Positive	NA	NA	NA	Chemotherapy	NA	Median survival time of 11 months*
Sabater et al.[7]	No PNS (11)	SCLC (11)	NA	Positive	NA	NA	NA	NA	NA	NA
Hardy-Werbin et al.[15]	NA	SCLC (22)	NA	Positive	NA	NA	NA	Chemotherapy	NA	NA
Tschernatsch et al.[46]	Neuropathy (2/2)	Bronchial carcinoid (1) SCLC (1)	56/M 61/M	Positive	NA	Subacute Chronic	NA	Tumor extirpation for bronchial carcinoid Chemotherapy	None	NA
Horta et al.[64]	NA	NA, mostly lung cancer (22)	NA	Positive	NA	NA	NA	NA	NA	NA
Zekeridou et al.[48]	PNS (10) No PNS (3)	SCLC (13)	NA	Positive	NA	NA	NA	NA	NA	NA
Vural et al.[47]	No PNS (17)	SCLC (17)	55.2 (mean), 12×M, 5×F	Positive	NA	NA	NA	All received chemotherapy and radiotherapy	None	Median survival time of 13 months. 2 SCLC patients progressed, 15 responded to therapy
Additional abs										
Case reports and series										
Kunstreich et al.[65]	SOX1, PCA2 (1) PLE, neuropathy	Mediastinal mass of Hodgkin's lymphoma (1)	17/M	Positive for both abs. Both abs negative after treatment	Positive for both abs at onset. Both abs negative after treatment	Recurrent symptoms, subacute	Medial temporal-lobe and limbic system with enhancement	Surgical excision, chemotherapy, and radiotherapy	Corticosteroids, IVIg, plasmapheresis, cyclophosphamide, azathioprine, and rituximab with subsequent oral prednisolone therapy (10 mg/day)	Temporarily improved before worsening after interruption of immunosuppression several times. At 5-year follow-up, walking with walking aids and orthoses. Spastic paresis, autonomic dysfunction, and polyneuropathy remained

Table 2. Anti-SOX1-abs-related clinical characteristics (continued)

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Fukuda et al.[55]	SOX1, Hu, amphiphysin (1) PLE	SCLC (1)	56/M	Positive for all abs	Positive for all abs	Subacute	Limbic system	Surgical excision, chemotherapy, and radiotherapy	Corticosteroids, IVIg, plasmapheresis, cyclophosphamide	Dead (time from onset NA)
Kacem et al.[51]	SOX1, Hu, $GABA_BR$ (1) PLE	SCLC (1)	53/M	Positive for all abs	NA	Acute	None	Chemotherapy	Oral corticosteroid	Progression-free survival for 7 months
Zuliani et al.[52]	SOX1, VGKC (2) PLE (2)	SCLC (2) (mediastinal mass)	47/M* Middle-aged/F	Positive for both abs	NA	Acute Subacute	Temporal lobes of male patient Normal MRI in female patient	Chemotherapy for the male patient. No therapy targeting the tumor in female patient	IV steroids for male patient. No immunotherapy given to female patient	Male patients died 11 months after PLE onset. Female patient died with date NA
Höftberger et al.[53]	SOX1, AMPAR, $GABA_BR$ (1) PLE with hyponatremia SOX1, AMPAR (1) PLE with hyponatremia	SCLC (2)	63/F 81/F	Positive for both abs	NA	Both subacute	One patient with medial temporal-lobe abnormality, other with bilateral temporal-lobe abnormality	Patients with 3 abs had chemotherapy and radiotherapy. Other patient had chemotherapy alone	The patient with 2 abs received corticosteroids therapy	Patient with 3 abs had partial response to treatment, and died during 16.25-month follow-up. Other patient did not respond to therapy and died during 30.75-month follow-up
Höftberger et al.[54]	SOX1, $GABA_BR$ (3) PLE (3)	SCLC (3)	60/M 68/F 74/M	Positive for both abs	NA	NA	NA	2 patients received chemotherapy, and 1 patient did not receive treatment	One patient with steroid and IVIg treatment	All died during 1.75-, 12-, and 1.5-month follow-ups
Boronat et al.[56]	SOX1, $GABA_BR$, VGKC (1) SOX1, $GABA_BR$, GAD65 (1)† Both PLE	SCLC (2)	47/M 70/M	Positive for all abs	NA	NA	Bilateral temporal lesions. Other patient with normal MRI	Both received chemotherapy	Both received steroids, IVIg	All died. One patient did not respond to treatment and died from cancer-related treatment 2 months later. One patient showed partial recovery, with relapsing course (died from cancer progression)

Table 2. Anti-SOX1-abs-related clinical characteristics (continued)

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Dogan Onugoren et al.[20]	SOX1, $GABA_BR$ (1) PLE with gait difficulties	NSCLC (1)	74/F	Positive for both abs	SOX1 (+) $GABA_BR$ (–)	NA	Unilateral mediotemporal lesion	Chemotherapy	Steroids, azathioprine	Improved memory 6 months later
Lai et al.[57]	SOX1, AMPAR, $VGCC_{P/Q}$ (1) PLE, mild dysdiadochokinesia, PCD, Raynaud's syndrome	SCLC (1)	59/F	Positive for all abs	NA	Subacute	Medial temporal lobes and medial orbitofrontal region	Tumor removal, chemotherapy	Corticosteroids, IVIg	Died from myocardial infarction
Dik et al.[61]	Initial: SOX1, Hu; polyneuropathy (CIDP). 7 months later: SOX1, Hu, Zic4; PLE. 11 months later: SOX1, Hu, Zic4, Yo; PLE, neuropathy, PCD. 29 months later: SOX1, Hu, Zic4, CV2/ CRMP5	SCLC (1)	70/M	Positive for all abs	Initial: negative for both abs. 7 and 11 months later: positive for all abs. 29 months later: positive for all abs except Yo	Chronic	Initial MRI of the brain and entire spinal cord showed moderate contrast enhancement in fibers of the cauda equina radices only. 7 months later showed bilateral temporomesial brain region abnormality	Radiochemotherapy	Methylprednisolone (IV and orally) Cyclophosphamide	Deteriorating memory and executive functions together with progressive sensory and also cerebellar ataxia and continued temporal-lobe seizures at 22-month follow up
Dubey et al.[66‖]	SOX1, CV2/CRMP5 (2) Neuropathy (2)	NA (2)	NA	Positive for all abs	NA	NA	NA	NA	NA	NA
Ge et al.[42]	SOX1, $VGCC_{P/Q}$ (1) LEMS, neuropathy	SCLC (1)	48/F	Positive for both abs	NA	Chronic	None	Chemotherapy	IVIg	Limb weakness partially recovered
Ueno et al.[58]	SOX1, Hu, AChR (1) Autonomic PNS	SCLC (1)	65/M	Positive for both abs	NA	Chronic	None	Chemotherapy	IVIg	Autonomic symptoms disappeared. Patient still alive 10 months later
Zhang et al.[59]	SOX1, GAD65 (1) LEMS	SCLC (1)	56/M	Positive for both abs	SOX1 (+) GAD65 (–)	Subacute	None	Chemotherapy	None	LEMS-associated symptoms partially relieved 2 months later
Research articles										
Graus et al.[6¶]	SOX1, $VGCC_{P/Q}$ (5) PCD	SCLC (5)	NA	Positive for both abs	NA	NA	NA	NA	NA	NA

Table 2. Anti-SOX1-abs-related clinical characteristics (continued)

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Sabater et al.[7¶]	SOX1, $VGCC_{P/Q}$ (35) [LEMS (35)] SOX1, Hu (16) [neuropathy (10), PCD (3), encephalomyelitis (2), PLE (1)]	SCLC (51)	NA	Positive for both abs	NA	NA	NA	NA	NA	NA
Titulaer et al.[11¶]	SOX1, $VGCC_{P/Q}$ (15); SOX1, Hu (17); SOX1, $VGCC_{P/Q}$, Hu (13) LEMS 60% (27), PCD (9), no PNS (18)	SCLC (45)	32–78 (range)*, 49×M, 23×F*	Positive for all abs	NA	NA	NA	4 patients without chemotherapy	NA	Median survival time of 15 months*
Hardy-Werbin et al.[15]	SOX1, Yo (3); SOX1, Hu (3); SOX1, GAD65 (1); SOX1, Hu, GAD65 (1); SOX1, Hu, Yo, amphiphysin (1) . Symptoms NA	SCLC (9)	NA	Positive for all abs	NA	NA	NA	All patients received chemotherapy	NA	NA
Sabater et al.[16]	SOX1, $VGCC_{P/Q}$ (10); SOX1, Hu (4); SOX1, Zic4 (1); SOX1, $VGCC_{P/Q}$, Hu (2); SOX1, $VGCC_{P/Q}$, Hu, Zic4 (1) PCD (18), LEMS (8)	SCLC (18)	NA	Positive for all abs	NA	NA	NA	NA	NA	NA
Titulaer et al.[49¶]	SOX1, $VGCC_{P/Q}$ (59)[§] LEMS (59), autonomic symptoms	SCLC (59)	NA	Positive for both abs	NA	NA	NA	NA	NA	NA
Tschernatsch et al.[46]	SOX1, Hu (3) Neuropathy (3/3)	SCLC (3)	72/F 75/M 81/F	Positive for both abs	NA	Subacute (2) Chronic (1)	NA	All patients received chemotherapy	2 patient received steroids, IVIg, azathioprine. 1 patient received plasma exchange	One patient reported slight improvement after plasma exchange. No improvement in other 2 patients
Horta et al.[64‖]	SOX1, $VGCC_{P/Q}$, $VGCC_N$, CV2/CRMP5 (1); SOX1, $VGCC_{P/Q}$, $VGCC_N$, Hu (1); SOX1, $VGCC_{P/Q}$, $VGCC_N$ (5); SOX1, $VGCC_{P/Q}$ (6); SOX1, $VGCC_N$ (3); SOX1, Hu (1)	NA	NA	Positive for all abs	NA	NA	NA	NA	NA	NA

Table 2. Anti-SOX1-abs-related clinical characteristics (continued)

Reference	Clinical neurological symptoms and other coexisting abs	Associated cancer (number of cases)	Age (years)/ sex	Serum anti-SOX1 abs	CSF anti-SOX1 abs	Disease course	MRI FLAIR/ T2-weighted increased signal	Treatment		Outcomes (times are from symptom onset)
								Treatment of tumor	Immunotherapy	
Zekeridou et al.[48]	SOX1, $VGCC_{P/Q}$ (2) LEMS (2)	SCLC (2)	NA	NA	NA	NA	NA	NA	NA	NA
Vural et al.[47]	SOX1, Zic2 (8) No PNS (8)	SCLC (8)	55 (mean), 8×F	Positive for all abs	NA	NA	NA	All patients received chemotherapy and radiotherapy	None	Median survival time of 26 months All patients responded to therapy
Jeffery et al.[60]	SOX1, $GABA_BR$ (1) PLE (1)	SCLC (1)	63/M	Positive for both abs	NA	NA	NA	Chemotherapy	None	Follow-up for 1 month. Half improved postchemotherapy, but with residual deficits
Stich et al.[21]	SOX1, Hu (5); SOX1, amphiphysin (1); SOX1, CV2/CRMP5 (1); SOX1, Hu, CV2/CRMP5 (1) PCD (2), neuropathy (5), encephalomyelitis (3), brainstem encephalitis (1), PLE (1)	SCLC (4) NSCLC (2) (polymorphic and undifferentiated neuroendocrinal)	47–70 (range), 4×M, 2×F	Positive for all abs	1 positive, 2 negative CSF positive for both SOX1 and Hu abs	NA	1 patient with encephalomyelitis and neuropathy showed longitudinal T2-weighted hyperintensity of the thoracic spinal cord; 2 patients with PCD showed cerebellar atrophy; 1 patient with PLE showed bilateral temporo-mesial and hippocampus abnormality; other 2 patients with brainstem encephalitis, neuropathy, and encephalomyelitis showed no abnormality	NA	NA	Median survival time of 38.5 months (range 25–155 months). Clinical outcome NA
No cancer	Graus et al. (2/41),[45] Berger et al. (10/15),[18] Ruiz-García et al. (2/71),[12] Titulaer et al. (2/72),[11] Titulaer et al. (6/65),[49] Stich et al. (2/8),[21] Dogan Onugoren et al. (2/3),[20] Tschernatsch et al. (4/9),[46] Sabater et al. (1/62),[7] Saraya et al. (2/2),[63] Alessandro et al. (1/1)[25]									

*Data analyzed based on all patients with anti-SOX1 abs including both anti-SOX1 abs alone and other coexisting onconeural abs, †Lancaster et al.[99] also reported a 70-year-old male patient with SOX1, GABABR, and GAD65. Considering that both studies involved researchers from the University of Pennsylvania, we did not include the patient from Lancaster et al., ‡Including the same patient without double counting, §In the study, 59 (56.8%) of 104 patients had SOX1 abs and 98 (94.3%) had VGCC abs among the SCLC-LEMS patients. No detailed information was available about coexisting abs between SOX1 and VGCC abs. Considering the high frequency of VGCC abs, we calculated all patients with SOX1 coexisting with VGCC abs, which might have resulted in minor statistical errors, ‖ Data may be overcounted due to studies based on the same Mayo Clinic database including patients from different years, ¶Data may be overcounted due to studies based on the same Dutch and Spanish databases including patients from different years.

abs: antibodies, AChR: acetylcholine receptor, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CIDP: chronic inflammatory demyelinating polyneuropathy, CRMP5: collapsin response-mediator protein-5, CSF: cerebrospinal fluid, F: female, FLAIR: fluid-attenuated inversion recovery, $GABA_BR$: γ-Aminobutyric acid-B receptor, GAD65: glutamate decarboxylase 65, IV: intravenous, IVIg: IV immunoglobulin, LEMS: Lambert-Eaton myasthenic syndrome, M: male, NA: data not available, NSCLC: non-SCLC, PCA: Purkinje cell ab type, PCD: paraneoplastic cerebellar degeneration, PLE: paraneoplastic limbic encephalitis, PNS: paraneoplastic neurological syndrome, SCLC: small-cell lung cancer, SOX: Sry-like high mobility group box, VGCC: voltage-gated calcium channel, VGKC: voltage-gated potassium channel, Zic: zinc-finger protein.

Table 3. Clinical and immunological data of patients with anti-SOX1 abs

Variable	*n* (%)
Total patients*	520 (100.0)
Clinical syndromes of patients with anti-SOX1 abs alone (*n*=110)	
PNS (*n*=116)†	
LEMS*	33 (30.0)
PCD	20 (18.2)
PLE	20 (18.2)
Neuropathy	9 (8.2)
Unidentified	34 (30.9)
Without PNS (*n*=78)	
Coexisting tumor	
Tumor (*n*=486)	
SCLC*	414 (85.2)
NSCLC	22 (4.5)
Squamous-cell cancer	6 (1.2)
Adenocarcinoma	7 (1.4)
Polymorphic	1 (0.2)
Bronchial carcinoid	1 (0.2)
Unspecified NSCLC	7 (1.4)
Other cancer	9 (1.9)
Breast cancer	3 (0.6)
Hodgkin's lymphoma	2 (0.4)
Prostate cancer	1 (0.2)
Thyroid cancer	1 (0.2)
Esophagus cancer	1 (0.2)
Multiple cancers (prostate, penis, cecum, liver, and NSCLC)	1 (0.2)
Unidentified coexisting tumor	41 (8.4)
Nontumor identified (*n*=34)	
Patients positive in serum or CSF for ≥1 abs (*n*=520)	
SOX1 alone*	275 (52.9)
2 autoabs	213 (41.0)
3 autoabs	27 (5.1)
4 autoabs	4 (0.8)
5 autoabs	1 (0.2)
Neuronal antigen (*n*=285)	
Coexisting intracellular antigens (*n*=103)	
Hu	73 (34.8)
Zic2	8 (3.8)
CV2/CRMP5*	6 (2.9)
Yo	5 (2.4)
GAD65	4 (1.9)
Amphiphysin	3 (1.4)
Zic4	3 (1.4)
PCA2	1 (0.5)
Coexisting cell-surface antigens (*n*=182)	
$VGCC_{P/Q}$	157 (86.3)
$VGCC_{N}$	10 (5.5)
$GABA_BR$	9 (5.0)
VGKC	3 (1.6)
AMPAR	3 (1.6)
CSF anti-SOX1 abs (*n*=17)	
Positive	13 (76.5)
Negative	4 (23.5)

*Data may be overcounted due to overlapping patients from the same database of the Mayo Clinic[64,66] and the Dutch and Spanish databases.[6,7,11,49], †There were 110 patients with anti-SOX1 abs alone and a total of 116 PNS patients due to coexisting PNS in some patients.[40-43]
AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CRMP5: collapsin response-mediator protein-5, CSF: cerebrospinal fluid, $GABA_BR$: γ-Aminobutyric acid-B receptor, GAD65: glutamate decarboxylase 65 LEMS: Lambert-Eaton myasthenic syndrome, NSCLC: non-SCLC, PCA: Purkinje cell ab type, PCD: paraneoplastic cerebellar degeneration, PLE: paraneoplastic limbic encephalitis, PNS: paraneoplastic neurological syndrome, SCLC: small-cell lung cancer, SOX: Sry-like high mobility group box, VGCC: voltage-gated calcium channel, VGKC: voltage-gated potassium channel, Zic: zinc-finger protein.

stituted one of the six cases of squamous-cell lung cancer. Abnormal DNA methylation of the promoter region of SOX1 is a potential pathogenesis.[19, 62]

Notably, a small group (*n*=34, 6.5%) of the 520 patients with anti-SOX1 abs developed neurological symptoms without underlying tumors,[7,11,12,18,20,21,25,45,46,49,63] even after years of follow-up, but the mechanism that triggered the autoimmune response remains unknown. A possible explanation is that the tumor was too small to be detected or would have developed in the future. In congruence with a recent study, in a patient with multiple autoabs (those to SOX1, Hu, Yo, Zic4, and CV2) but without tumor identification, SCLC was confirmed until 30 months after disease onset.[61] Furthermore, despite the follow-up lasting up to 15 years and being a median of 7 years, we cannot exclude the possibility that some cancer-negative patients had an occult neoplasm owing to the absence of cancer checkups in most patients.[18,49] Therefore, autoabs alone were not sufficient for differentiating cancer-positive from cancer-negative patients.

Other coexisting neural autoabs

Coexisting neuronal autoabs were not uncommon in patients with anti-SOX1 abs. Frequencies of the coexistence of anti-SOX1 abs with other neuronal autoabs exceeded the frequencies previously assumed for PNS. A previous study of 9,183 PNS patients with identified autoabs revealed the coexistence of multiple antineuronal abs in 17% of them.[64] Additionally, 28% of 85 SCLC patients compared with 18% of 210 NSCLC patients had more than 1 ab.[15,64] In the current review, 245 (47.1%) of the 520 patients showed the coexistence of multi-

ple onconeuronal and cell-surface autoabs at any time point: 213 (41.0%) patients had 2 autoabs,[6,7,11,15,16,20,21,42,46-49,52-55,59,60,64-66] 27 (5.1%) patients had 3 autoabs,[11,15,16,51,53,56-58,64] 4 (0.8%) patients had 4 autoabs,[15,16,21,64] and 1 (0.2%) patient had 5 autoabs.[61] In the 285 patients with additional autoabs coexisting with anti-SOX1 abs, anti-VGCC$_{P/Q}$ (n=157, 55.1%)[6,7,11,16,42,48,49,57,64] and anti-Hu (n=73, 25.6%)[7,11,15,16,21,46,51,55,58,61,64] abs were the most common (Table 3).

Most of the present patients had SCLC, with only one having Hodgkin's lymphoma[65] and three patients having NSCLC.[20,21] On the other hand, 53.4% (n=221) of the 414 SCLC patients with anti-SOX1 abs exhibited multireactivity. The presence of coexisting autoabs reflects a multifaceted response to the diverse immunogenic proteins expressed in tumors, and it is conceivable that clusters of autoabs are explained by a tumor causing mutagenic processes.[64,67] The presence of multiple autoabs coexisting with anti-SOX1 abs could be a stronger predictor of an SCLC diagnosis than the presence of only anti-SOX1 abs.[64,68]

Among the anti-SOX1 abs patients with coexisting neuronal autoabs, 11 with additional autoabs to cell-surface proteins [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and γ-aminobutyric acid-B receptor (GABA$_B$R)] had a high probability of developing syndromes influenced by the additional autoabs: all patients had PLE, which is typical of anti-AMPAR or GABA$_B$R autoimmune syndrome.[69]

The presence of multiple autoabs in patients—including antineuronal abs (e.g., anti-Hu, anti-Yo, and anti-amphiphysin) and cell-surface abs (anti-AMPAR and anti-GABA$_B$R)—is associated with multiple coexisting PNS components and a worse prognosis compared with the presence of a single autoab. Multiple autoabs were present in 79% (n=11) of the 14 patients with anti-SOX1 abs who died. Consistent with our findings, Hardy-Werbin et al.[15] suggested that the presence of a single autoab in SCLC was associated with a better outcome in SCLC patients than the presence of multiple autoabs. Multiple cytotoxic T-cell mechanisms mediated by autoabs might influence the outcome in patients with onconeuronal autoabs. These findings suggest that the coexistence of additional paraneoplastic autoimmunity is also a potential predictor of a poor clinical outcome. In addition, attention still needs to be paid to the case reports of only anti-SOX1 abs being present in patients with a relatively short follow-up period, which may lead to statistical errors.[17,41]

Anti-SOX1 abs in the cerebrospinal fluid

In most cases of PNS associated with cell-surface abs (e.g., abs against the N-methyl-d-aspartate receptor), there is a significant clinical immunological correlation between antigen-specific intrathecal humoral immune responses and the presence of symptoms, supporting the hypothesis of autoimmunity being involved in the pathogenesis.[5] In contrast, PNS associated with onconeuronal autoabs such as anti-SOX1 abs is mediated by cytotoxic T-cell mechanisms.[5] In addition, a previous study analyzed 489 patients with a clinical suspicion of PNS for the presence of well-characterized onconeural abs.[70] Only 18 patients (3.7%) presented positive autoabs in the cerebrospinal fluid (CSF) and 10 of the 15 patients affected by PNS involving the central nervous system showed the intrathecal synthesis of onconeural abs. Therefore, although the intrathecal synthesis of onconeural abs has been found in a few patients, the common consensus is that the presence of onconeural autoabs is predictive of a tumor. However, there is a lack of exhaustive studies to confirm a direct pathogenic role.

The present review found that most of anti-SOX1 abs were identified in serum, in addition to 10 patients identified by applying immunohistochemistry to biopsy specimens.[19] Paired CSF and serum samples were available for only 17 patients with SOX1 reactivity.[6,20,21,25,55,59,61,63,65] Among them, 4 patients were negative for anti-SOX1 abs in the CSF,[21,25] while the other 13 patients showed positive anti-SOX1 abs reactivity in the CSF.[6,20,21,55,57,61,63,65]

Neuroimaging features

According to the commonly accepted diagnostic criteria of PCD from the Euronetwork in 2004,[71] there should be no MRI evidence of cerebellar atrophy for severe PCD within 12 weeks, other than what would be expected given the age of a patient. Indeed, the initial MRI findings have been normal in most PCD patients,[22] although there have also been reports of diffuse cerebellar enlargement.[72] At present, the consensus is that most PCD patients do not have abnormal cerebellar signals on MRI, and some [(18)F]fluoro-deoxyglucose positron-emission tomography (18F-FDG PET) findings have revealed the manifestation of cerebellar hypermetabolism in the early stage of PCD.[73] As time passes, MRI may show cerebellar atrophy, while 18F-FDG PET shows hypometabolism.

Brain or spinal MRI data were available for 30 patients with anti-SOX1 abs in this review. The proportions of cases with normal and abnormal MRI findings for anti-SOX1 abs were very similar, with 46.7% of the patients (n=14) showing normal findings regardless of the follow-up time.[17,21,40,42-44,51,52,56,58,59] Abnormal cerebellar changes were observed in only 3 of the 30 patients with anti-SOX1 abs:[21,25] 2 patients with PCD had cerebellar atrophy[21] and 1 patient with PCD had diffuse hyperintense lesions in T2-weighted imaging of the cerebellum and brainstem.[25]

In general, 46.7% of the patients (*n*=14) showed brain lesions,[12,20,21,25,45,55,56,61,65] with 11 patients having PLE and 3 having PCD.[20,21,45,51,53,55-57,61,65] In addition, 10.0% of the patients (*n*=3) had spinal lesions.[21,40,61] Among all patients with abnormal lesions, one showed both brain and spinal lesions,[61] and only three patients had anti-SOX abs alone;[25,40,45] therefore, we cannot exclude the possibility that the lesions were caused by additional coexisting autoabs.

Treatment and clinical outcomes

The extremely low prevalence of anti-SOX1-abs-related PNS has prevented randomized controlled trials, and hence there are no evidence-based guidelines for treatment. Therapeutic management was mentioned for 29.6% (*n*=154) of the 520 patients reported in the literature. Almost all of these patients (99.4%, *n*=153) were therapeutically managed using one or more of the following oncological treatments: tumor resection, chemotherapy, or radiotherapy. In combination with anticancer treatment, 20 (13.1%) patients also received first-line immunotherapy (corticosteroids, plasmapheresis, or intravenous immunoglobulin) or second-line immunotherapy (azathioprine, cyclophosphamide, or rituximab) (Table 2). Only one patient who presented with PCD without underlying cancer during the 3 years of follow-up received corticosteroids alone.[25]

These therapeutic interventions led to improvement in the neurological symptoms in 34% (*n*=32) of the 94 patients for whom therapeutic outcomes were reported. The follow-up time ranged from 15 days to 29 months.[17,20,41,46,47,58-60,66] The neurological symptoms did not improve in 10 patients.[25,42,44,46,47,51,61,65] Among the other patients with or without treatment, 14 died during a follow-up of up to 30.75 months,[40,43,45,52-57] all of whom were SCLC patients.

PNS is often therapy-refractive and relentlessly progressive. From the perspective of PCD, most patients have a generally poor clinical prognosis. Anti-neoplasm therapy and immunotherapies provide no benefit to most patients,[22] and no more than 10% of patients with PCD are thought to respond to immunotherapy following removal of the neoplasms.[74] This is likely to reflect the early and irreversible destruction of Purkinje cells. However, Mitoma et al.[22] proposed the therapeutic principle of "time is cerebellum" in IMCAs for the greatest level of improvement in cerebellar ataxia and the resilience of the cerebellar networks, which emphasized the priority of eliminating antigens, such as removing the primary tumor and the early administration of immunotherapy treatment. The early introduction of treatment during the period of so-called cerebellar reserve—defined as mild cerebellar atrophy and retention of the compensation capacity—is crucially important for preventing immune-mediated reactions and the cessation of oncological progression, which are thought to be correlated with a better prognosis.

It is noteworthy that some studies have suggested the presence of paraneoplastic autoimmunity in patients with anti-SOX1 abs, indicating an efficient antitumor immune response. The presence and higher titers of anti-SOX1 abs seem to be associated with better therapeutic responses in patients with SCLC.[47] However, further consistent findings have not been reported. There is a general tendency for patients with NSCLC and non-lung tumors to have better clinical outcomes, given that all of the summarized deceased patients were found to have SCLC. There is also increasing evidence that neither the presence nor the absence of anti-SOX1 abs is correlated with survival in SCLC,[11,48,75] and so we speculate that the prognosis of patients is largely determined by the original tumor type. The median survival time from the diagnosis of SCLC was shorter than 1 year, and the overall survival rate at 5 years was less than 10% due to its early metastasis.[76] The current study identified only one patient with squamous-cell lung cancer with a clinical outcome, and he fully recovered from PLE after 15 days of treatment without further follow-up.[17]

In general, PNS in association with anti-SOX1 abs remains a therapeutic challenge, with the main beneficial interventions being stabilization of the neurological deficits, while symptomatic amelioration was only observed in subsets of patients.

CONCLUSIONS

This review of the clinical features of patients with anti-SOX1 abs has several practical implications. First, in patients with LEMS and PCD, determining whether anti-SOX1 abs are present could be useful for localizing underlying malignancy. Second, the presence of a tumor (especially SCLC) should be suspected in anti-SOX1-abs-related PNS in older patients as well as in those who have additional abs. Meanwhile, anti-SOX1 abs also exist in NSCLC and non-lung cancers. Third, regular follow-up in order to maximize the ability to detect potential cancer is crucial for cancer-negative patients with anti-SOX1 abs. Fourth, applying immediate oncological treatment and immunotherapy is important, although the therapeutic effect of immunotherapy requires further validation. Fifth, a higher malignancy grade of the primary tumor and the presence of additional paraneoplastic autoabs seem to be the main prognostic factors for a poor outcome.

The main gaps in current studies are related to the incompleteness of clinical data for some patients, which may have resulted in the wide variation among the patients included in our analysis. Further studies that analyze comprehensive data on anti-SOX1 abs are needed. However, our study is the first review to fully describe the clinical characteristics of anti-SOX1

abs and their relationship with LEMS and PCD. We have provided practical information that clinicians can utilize in the differential diagnosis of PCD and neurological syndromes with positivity for anti-SOX1 abs.

Author Contributions

Conceptualization: Zhenfu Wang. Data curation: Xuan Sun, Yan Liu, Jiping Tan, Hui Sun. Supervision: Weiping Guan, Jianjun Jia. Writing—original draf: Xuan Sun, Jiping Tan, Hui Sun. Writing—review & editin: Weiping Guan, Jianjun Jia, Zhenfu Wang.

ORCID iDs

Xuan Sun	https://orcid.org/0000-0002-6894-3342
Jiping Tan	https://orcid.org/0000-0003-1121-9975
Hui Sun	https://orcid.org/0000-0001-8748-6880
Yan Liu	https://orcid.org/0000-0002-1313-9883
Weiping Guan	https://orcid.org/0000-0002-3955-5826
Jianjun Jia	https://orcid.org/0000-0002-0747-4132
Zhenfu Wang	https://orcid.org/0000-0002-1394-4962

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

None.

REFERENCES

1. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. *Lancet Neurol* 2008;7:327-340.
2. Iorio R, Smitt PS. Paraneoplastic cerebellar degeneration. In: Gruol DL, Koibuchi N, Manto M, Molinari M, Schmahmann JD, Shen Y, editors. *Essentials of cerebellum and cerebellar disorders.* Cham: Springer, 2016;587-593.
3. Bentea G, Sculier C, Grigoriu B, Meert AP, Durieux V, Berghmans T, et al. Autoimmune paraneoplastic syndromes associated to lung cancer: a systematic review of the literature: Part 3: neurological paraneoplastic syndromes, involving the central nervous system. *Lung Cancer* 2017;106:83-92.
4. Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. *Arch Neurol* 2010;67:330-335.
5. Dalmau J, Graus F. Antibody-Mediated Encephalitis. *N Engl J Med* 2018;378:840-851.
6. Graus F, Vincent A, Pozo-Rosich P, Sabater L, Saiz A, Lang B, et al. Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. *J Neuroimmunol* 2005;165:166-171.
7. Sabater L, Titulaer M, Saiz A, Verschuuren J, Güre AO, Graus F. SOX1 antibodies are markers of paraneoplastic Lambert-Eaton myasthenic syndrome. *Neurology* 2008;70:924-928.
8. Wegner M. From head to toes: the multiple facets of Sox proteins. *Nucleic Acids Res* 1999;27:1409-1420.
9. Schepers GE, Teasdale RD, Koopman P. Twenty pairs of Sox: extent, homology, and nomenclature of the mouse and human Sox transcription factor gene families. *Dev Cell* 2002;3:167-170.
10. Malas S, Duthie SM, Mohri F, Lovell-Badge R, Episkopou V. Cloning and mapping of the human SOX1: a highly conserved gene expressed in the developing brain. *Mamm Genome* 1997;8:866-868.
11. Titulaer MJ, Klooster R, Potman M, Sabater L, Graus F, Hegeman IM, et al. SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: frequency and relation with survival. *J Clin Oncol* 2009;27:4260-4267.
12. Ruiz-García R, Martínez-Hernández E, García-Ormaechea M, Español-Rego M, Sabater L, Querol L, et al. Caveats and pitfalls of SOX1 autoantibody testing with a commercial line blot assay in paraneoplastic neurological investigations. *Front Immunol* 2019;10:769.
13. Kanaji N, Watanabe N, Kita N, Bandoh S, Tadokoro A, Ishii T, et al. Paraneoplastic syndromes associated with lung cancer. *World J Clin Oncol* 2014;5:197-223.
14. Güre AO, Stockert E, Scanlan MJ, Keresztes RS, Jäger D, Altorki NK, et al. Serological identification of embryonic neural proteins as highly immunogenic tumor antigens in small cell lung cancer. *Proc Natl Acad Sci U S A* 2000;97:4198-4203.
15. Hardy-Werbin M, Arpí O, Taus A, Rocha P, Joseph-Pietras D, Nolan L, et al. Assessment of neuronal autoantibodies in patients with small cell lung cancer treated with chemotherapy with or without ipilimumab. *Oncoimmunology* 2017;7:e1395125.
16. Sabater L, Höftberger R, Boronat A, Saiz A, Dalmau J, Graus F. Antibody repertoire in paraneoplastic cerebellar degeneration and small cell lung cancer. *PLoS One* 2013;8:e60438.
17. Cho HJ, Kim R, Lee HW, Jun JS. Encephalitis with anti-SOX1 antibodies presenting with new-onset refractory status epilepticus. *J Clin Neurol* 2019;15:564-565.
18. Berger B, Dersch R, Ruthardt E, Rasiah C, Rauer S, Stich O. Prevalence of anti-SOX1 reactivity in various neurological disorders. *J Neurol Sci* 2016;369:342-346.
19. Li N, Li S. Epigenetic inactivation of SOX1 promotes cell migration in lung cancer. *Tumour Biol* 2015;36:4603-4610.
20. Dogan Onugoren M, Deuretzbacher D, Haensch CA, Hagedorn HJ, Halve S, Isenmann S, et al. Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. *J Neurol Neurosurg Psychiatry* 2015;86:965-972.
21. Stich O, Klages E, Bischler P, Jarius S, Rasiah C, Voltz R, et al. SOX1 antibodies in sera from patients with paraneoplastic neurological syndromes. *Acta Neurol Scand* 2012;125:326-331.
22. Mitoma H, Manto M, Hampe CS. Immune-mediated cerebellar ataxias: practical guidelines and therapeutic challenges. *Curr Neuropharmacol* 2019;17:33-58.
23. Hadjivassiliou M. Immune-mediated acquired ataxias. *Handb Clin Neurol* 2012;103:189-199.
24. Shams'ili S, Grefkens J, de Leeuw B, van den Bent M, Hooijkaas H, van der Holt B, et al. Paraneoplastic cerebellar degeneration associated with antineuronal antibodies: analysis of 50 patients. *Brain* 2003;126:1409-1418.
25. Alessandro L, Schachter D, Farez MF, Varela F. Cerebellar ataxia with extreme photophobia associated with anti-sox1 antibodies. *Neurohospitalist* 2019;9:165-168.
26. Alcock J, Lowe J, England T, Bath P, Sottile V. Expression of Sox1, Sox2 and Sox9 is maintained in adult human cerebellar cortex. *Neurosci Lett* 2009;450:114-116.
27. Alcock J, Sottile V. Dynamic distribution and stem cell characteristics of Sox1-expressing cells in the cerebellar cortex. *Cell Res* 2009;19:1324-1333.
28. Venkatraman A, Opal P. Paraneoplastic cerebellar degeneration with anti-Yo antibodies-a review. *Ann Clin Transl Neurol* 2016;3:655-663.
29. Mitoma H, Manto M, Hampe CS. Immune-mediated cerebellar ataxias: from bench to bedside. *Cerebellum Ataxias* 2017;4:16.
30. Ducray F, Demarquay G, Graus F, Decullier E, Antoine JC, Giometto B, et al. Seronegative paraneoplastic cerebellar degeneration: the PNS Euronetwork experience. *Eur J Neurol* 2014;21:731-735.
31. Hasadsri L, Lee J, Wang BH, Yekkirala L, Wang M. Anti-Yo associated paraneoplastic cerebellar degeneration in a man with large cell cancer of the lung. *Case Rep Neurol Med* 2013;2013:725936.
32. Huemer F, Melchardt T, Tränkenschuh W, Neureiter D, Moser G, Magnes T, et al. Anti-Hu antibody associated paraneoplastic cerebellar degeneration in head and neck cancer. *BMC Cancer* 2015;15: 996.
33. Graus F, Lang B, Pozo-Rosich P, Saiz A, Casamitjana R, Vincent A. P/Q type calcium-channel antibodies in paraneoplastic cerebellar de-

generation with lung cancer. *Neurology* 2002;59:764-766.
34. Cai G, Sun X, Yu J, Meng X, Li J. Non-small cell lung cancer associated with late-onset Lambert-Eaton myasthenic syndrome and paraneoplastic cerebellar degeneration. *Neurol Sci* 2020;41:1277-1279.
35. Bruylant K, Crols R, Humbel RL, Appel B, De Deyn PP. Probably anti-Tr associated paraneoplastic cerebellar degeneration as initial presentation of a squamous cell carcinoma of the lung. *Clin Neurol Neurosurg* 2006;108:415-417.
36. Sabater L, Bataller L, Carpentier AF, Aguirre-Cruz ML, Saiz A, Benyahia B, et al. Protein kinase Cgamma autoimmunity in paraneoplastic cerebellar degeneration and non-small-cell lung cancer. *J Neurol Neurosurg Psychiatry* 2006;77:1359-1362.
37. Hiasa Y, Kunishige M, Mitsui T, Kondo S, Kuriwaka R, Shigekiyo S, et al. Complicated paraneoplastic neurological syndromes: a report of two patients with small cell or non-small cell lung cancer. *Clin Neurol Neurosurg* 2003;106:47-49.
38. Konishi J, Yamazaki K, Chikai K, Nagashima K, Sakai K, Kinoshita I, et al. Paraneoplastic cerebellar degeneration (PCD) associated with squamous cell carcinoma of the lung. *Intern Med* 2004;43:602-606.
39. Day J, Yan B, Boer RD, Tsui A. Paraneoplastic cerebellar degeneration associated with squamous cell carcinoma of the lung. *J Clin Neurosci* 2013;20:1448-1449.
40. Li C, Wang X, Sun L, Deng H, Han Y, Zheng W. Anti-SOX1 antibody-positive paraneoplastic neurological syndrome presenting with Lambert-Eaton myasthenic syndrome and small cell lung cancer: a case report. *Thorac Cancer* 2020;11:465-469.
41. Mirallas O, Rial N, Martín-Cullell B, Recio-Iglesias J. A rare case of long-term paraesthesia diagnosed as a paraneoplastic syndrome by anti-SOX1 antibody determination. *BMJ Case Rep* 2019;12:e228916.
42. Ge FF, Li MX, Ruan Z, Chang T, Liu Y, Li HH, et al. [Clinical, electrophysiological profile and prognosis in paraneoplastic syndrome with SRY-like high-mobility group superfamily of developmental transcription factors 1 antibody.] *Chin J Neurol* 2019;52:104-109.
43. Liu L, Ma QY, Kang WT, Yu D, Qiao ZX, Jing Y, et al. [A case of myasthenia gravis as a paraneoplastic syndrome and sensory peripheral neuropathy with anti-SOX1 antibodies.] *Chin J Neurol* 2017;50:683-685.
44. Ji MH, Bai SF, Zhai MM, Cheng LN. [Paraneoplastic cerebellar degeneration in anti-SOX1 antibodies: a case report and literature review.] *J Apoplexy Nerv Dis* 2019;7:651-653.
45. Graus F, Saiz A, Lai M, Bruna J, López F, Sabater L, et al. Neuronal surface antigen antibodies in limbic encephalitis: clinical-immunologic associations. *Neurology* 2008;71:930-936.
46. Tschernatsch M, Singh P, Gross O, Gerriets T, Kneifel N, Probst C, et al. Anti-SOX1 antibodies in patients with paraneoplastic and non-paraneoplastic neuropathy. *J Neuroimmunol* 2010;226:177-180.
47. Vural B, Chen LC, Saip P, Chen YT, Ustuner Z, Gonen M, et al. Frequency of SOX Group B (SOX1, 2, 3) and ZIC2 antibodies in Turkish patients with small cell lung carcinoma and their correlation with clinical parameters. *Cancer* 2005;103:2575-2583.
48. Zekeridou A, Majed M, Heliopoulos I, Lennon VA. Paraneoplastic autoimmunity and small-cell lung cancer: neurological and serological accompaniments. *Thorac Cancer* 2019;10:1001-1004.
49. Titulaer MJ, Maddison P, Sont JK, Wirtz PW, Hilton-Jones D, Klooster R, et al. Clinical Dutch-English Lambert-Eaton myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. *J Clin Oncol* 2011;29:902-908.
50. Zoccarato M, Gastaldi M, Zuliani L, Biagioli T, Brogi M, Bernardi G, et al. Diagnostics of paraneoplastic neurological syndromes. *Neurol Sci* 2017;38:237-242.
51. Kacem M, Belloumi N, Bachouche I, Mersni M, Chermiti Ben Abdallah F, Fenniche S. Paraneoplastic limbic encephalitis revealing a small cell carcinoma of the lung. *Respir Med Case Rep* 2018;26:157-160.
52. Zuliani L, Saiz A, Tavolato B, Giometto B, Vincent A, Graus F. Paraneoplastic limbic encephalitis associated with potassium channel antibodies: value of anti-glial nuclear antibodies in identifying the tumour. *J Neurol Neurosurg Psychiatry* 2007;78:204-205.
53. Höftberger R, van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, et al. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. *Neurology* 2015;84:2403-2412.
54. Höftberger R, Titulaer MJ, Sabater L, Dome B, Rózsás A, Hegedus B, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. *Neurology* 2013;81:1500-1506.
55. Fukuda TG, do Rosário MS, Branco RCC, Fukuda JS, de Souza E Souza RA, Oliveira-Filho J, et al. Multiple paraneoplastic antibodies (anti-SOX1, anti-Hu, and anti-Amphiphysin) detected in a patient with limbic encephalitis and small cell lung cancer. *Neurol India* 2017;65:1127-1128.
56. Boronat A, Sabater L, Saiz A, Dalmau J, Graus F. GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. *Neurology* 2011;76:795-800.
57. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol* 2009;65:424-434.
58. Ueno T, Hasegawa Y, Hagiwara R, Kon T, Nunomura JI, Tomiyama M. Integrated treatment for autonomic paraneoplastic syndrome improves performance status in a patient with small lung cell carcinoma: a case report. *BMC Neurol* 2018;18:189.
59. Zhang YT, Li RL, Liu ZH, Dong HQ. [A case of cancerous Lambert-Eaton syndrome with SOXl antibody positive.] *J Neurosci Ment Health* 2016;16:735-737.
60. Jeffery OJ, Lennon VA, Pittock SJ, Gregory JK, Britton JW, McKeon A. GABAB receptor autoantibody frequency in service serologic evaluation. *Neurology* 2013;81:882-887.
61. Dik A, Strippel C, Mönig C, Golombeck KS, Schulte-Mecklenbeck A, Wiendl H, et al. Onconeural antigen spreading in paraneoplastic neurological disease due to small cell lung cancer. *Oxf Med Case Reports* 2018;2018:omy034.
62. Nelson HH, Marsit CJ, Christensen BC, Houseman EA, Kontic M, Wiemels JL, et al. Key epigenetic changes associated with lung cancer development: results from dense methylation array profiling. *Epigenetics* 2012;7:559-566.
63. Saraya AW, Worachotsueptrakun K, Vutipongsatorn K, Sonpee C, Hemachudha T. Differences and diversity of autoimmune encephalitis in 77 cases from a single tertiary care center. *BMC Neurol* 2019;19:273.
64. Horta ES, Lennon VA, Lachance DH, Jenkins SM, Smith CY, McKeon A, et al. Neural autoantibody clusters aid diagnosis of cancer. *Clin Cancer Res* 2014;20:3862-3869.
65. Kunstreich M, Kreth JH, Oommen PT, Schaper J, Karenfort M, Aktas O, et al. Paraneoplastic limbic encephalitis with SOX1 and PCA2 antibodies and relapsing neurological symptoms in an adolescent with Hodgkin lymphoma. *Eur J Paediatr Neurol* 2017;21:661-665.
66. Dubey D, Lennon VA, Gadoth A, Pittock SJ, Flanagan EP, Schmeling JE, et al. Autoimmune CRMP5 neuropathy phenotype and outcome defined from 105 cases. *Neurology* 2018;90:e103-e110.
67. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013;39:1-10.
68. McKeon A, Pittock SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. *Acta Neuropathol* 2011;122:381-400.
69. Grativvol RS, Cavalcante WCP, Castro LHM, Nitrini R, Simabukuro MM. Updates in the Diagnosis and Treatment of Paraneoplastic Neurologic Syndromes. *Curr Oncol Rep* 2018;20:92.
70. Corsini E, Gaviani P, Chiapparini L, Lazzaroni M, Ciusani E, Bisogno R, et al. Intrathecal synthesis of onconeural antibodies in patients with paraneoplastic syndromes. *J Neuroimmunol* 2016;290:119-122.
71. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135-1140.
72. de Andrés C, Esquivel A, de Villoria JG, Graus F, Sánchez-Ramón S. Unusual magnetic resonance imaging and cerebrospinal fluid find-

ings in paraneoplastic cerebellar degeneration: a sequential study. *J Neurol Neurosurg Psychiatry* 2006;77:562-563.
73. Choi KD, Kim JS, Park SH, Kim YK, Kim SE, Smitt PS. Cerebellar hypermetabolism in paraneoplastic cerebellar degeneration. *J Neurol Neurosurg Psychiatry* 2006;77:525-528.
74. Mitoma H, Hadjivassiliou M, Honnorat J. Guidelines for treatment of immune-mediated cerebellar ataxias. *Cerebellum Ataxias* 2015;2:14.
75. Lipka AF, Verschuuren JJ, Titulaer MJ. SOX1 antibodies in Lambert-Eaton myasthenic syndrome and screening for small cell lung carcinoma. *Ann N Y Acad Sci* 2012;1275:70-77.
76. Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, et al. PL02.11 Overall survival with durvalumab plus etoposide-platinum in first-line extensive-stage SCLC: results from the CASPIAN study. *J Thorac Oncol* 2019;14:S7-S8.
77. Le May M, Dent S. 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* 2018;25:e585-e591.
78. Finsterer J, Voigtländer T, Grisold W. Deterioration of anti-Yo-associated paraneoplastic cerebellar degeneration. *J Neurol Sci* 2011;308:139-141.
79. Debes JD, Lagarde SM, Hulsenboom E, Sillevis Smitt PA, ten Kate FJ, Sulter GA, et al. Anti-Yo-associated paraneoplastic cerebellar degeneration in a man with adenocarcinoma of the gastroesophageal junction. *Dig Surg* 2007;24:395-397.
80. Meglic B, Graus F, Grad A. Anti-Yo-associated paraneoplastic cerebellar degeneration in a man with gastric adenocarcinoma. *J Neurol Sci* 2001;185:135-138.
81. Sutton IJ, Fursdon Davis CJ, Esiri MM, Hughes S, Amyes ER, Vincent A. Anti-Yo antibodies and cerebellar degeneration in a man with adenocarcinoma of the esophagus. *Ann Neurol* 2001;49:253-257.
82. Matschke J, Kromminga A, Erbersdobler A, Lamszus K, Anders S, Köfüncü E. Paraneoplastic cerebellar degeneration and anti-Yo antibodies in a man with prostatic adenocarcinoma. *J Neurol Neurosurg Psychiatry* 2007;78:775-777.
83. Tanriverdi O, Meydan N, Barutca S, Ozsan N, Gurel D, Veral A. Anti-Yo antibody-mediated paraneoplastic cerebellar degeneration in a female patient with pleural malignant mesothelioma. *Jpn J Clin Oncol* 2013;43:563-568.
84. Mirouse A, Gobert D, Chamouard JM, Iordache L, Mekinian A, Fain O. Sudden death occurring after anti-Hu associated paraneoplastic cerebellar degeneration and dysautonomia revealing a small cell lung carcinoma. *Rev Med Interne* 2014;35:757-759.
85. Storstein A, Raspotnig M, Vitaliani R, Giometto B, Graus F, Grisold W, et al. Prostate cancer, Hu antibodies and paraneoplastic neurological syndromes. *J Neurol* 2016;263:1001-1007.
86. Tsukamoto T, Mochizuki R, Mochizuki H, Noguchi M, Kayama H, Hiwatashi M, et al. Paraneoplastic cerebellar degeneration and limbic encephalitis in a patient with adenocarcinoma of the colon. *J Neurol Neurosurg Psychiatry* 1993;56:713-716.
87. de la Sayette V, Bertran F, Honnorat J, Schaeffer S, Iglesias S, Defer G. Paraneoplastic cerebellar syndrome and optic neuritis with anti-CV2 antibodies: clinical response to excision of the primary tumor. *Arch Neurol* 1998;55:405-408.
88. Honnorat J, Cartalat-Carel S, Ricard D, Camdessanche JP, Carpentier AF, Rogemond V, et al. 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* 2009;80:412-416.
89. Aliprandi A, Terruzzi A, Rigamonti A, Bazzigaluppi E, Tremolizzo L, Ferrarese C, et al. Paraneoplastic cerebellar degeneration with anti-CV2/CRMP5 antibodies and prostate adenocarcinoma. *Neurol Sci* 2015;36:1501-1503.
90. Brieva-Ruíz L, Diaz-Hurtado M, Matias-Guiu X, Márquez-Medina D, Tarragona J, Graus F. Anti-Ri-associated paraneoplastic cerebellar degeneration and breast cancer: an autopsy case study. *Clin Neurol Neurosurg* 2008;110:1044-1046.
91. Bazine A, Fetohi M, Berri MA, Oufroukhi Y, Ichou M, Errihani H. Occult breast carcinoma presenting with anti-Ri-associated paraneoplastic cerebellar degeneration revealed with FDG-PET. *Cancer Clin Oncol* 2014;4:9-13.
92. Mancuso M, Orsucci D, Bacci A, Caldarazzo Ienco E, Siciliano G. Anti-Ri-associated paraneoplastic cerebellar degeneration. Report of a case and revision of the literature. *Arch Ital Biol* 2011;149:318-322.
93. Ameneiros-Lago E, Fernández-Fernández FJ, Lijó-Carballeda C. Paraneoplastic cerebellar degeneration associated with anti-Ma2 antibodies. *Med Clin (Barc)* 2016;147:e55-e56.
94. Bataller L, Wade DF, Graus F, Stacey HD, Rosenfeld MR, Dalmau J. Antibodies to Zic4 in paraneoplastic neurologic disorders and small-cell lung cancer. *Neurology* 2004;62:778-782.
95. Sabater L, Bataller L, Suárez-Calvet M, Saiz A, Dalmau J, Graus F. ZIC antibodies in paraneoplastic cerebellar degeneration and small cell lung cancer. *J Neuroimmunol* 2008;201-202:163-165.
96. Pavolucci L, Giannini G, Giannoccaro MP, Foschini MP, Lang B, Avoni P, et al. Paraneoplastic cerebellar degeneration and lambert-eaton myasthenia in a patient with merkel cell carcinoma and voltage-gated calcium channel antibodies. *Muscle Nerve* 2017;56:998-1000.
97. Zhang C, Emery L, Lancaster E. Paraneoplastic cerebellar degeneration associated with noncutaneous Merkel cell carcinoma. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e17.
98. Sillevis Smitt P, Kinoshita A, De Leeuw B, Moll W, Coesmans M, Jaarsma D, et al. Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. *N Engl J Med* 2000;342:21-27.
99. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010;9:67-76.