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 SOX1 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 neuropathy.4 PCD is the most common PNS and originates from autoimmune
damage to the cerebellum. 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). 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. 

Two types of PNS autoabs are classified based on the target antigen location: intracellular (onconeural) targets and cell-surface targets. In recent decades, the detection of well-characterized onconeural 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. 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 asso- 

nation of neoplasms in 70% of PCD patients. Cerebellar ataxia is the first manifestation of neoplasms 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. 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. 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. Cerebellar ataxia is the first manifestation of neoplasms in 70% of PCD patients.

#### 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) autoabs; and cell-surface (synaptic or plasma membrane) autoabs such as voltage-gated calcium channel (VGCC) (IP/ Q type), Tr, and mGlur1 autoabs (Table 1). Among them, anti-Yo autoabs are the most common.

Studies performed over the past 15 years have revealed the presence of PCD in patients with anti-SOX1 abs, 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.

#### Associated tumors

PCD generally predates a cancer diagnosis. Cerebellar ataxia occurs before the tumor has been detected in nearly 30%
| 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 PLE2,17,55,56 | SCLC,7,12,16,44,44 NSCLC (squamous-cell lung cancer) (Sun et al.)                                      |
| Anti-Yo             | PCD, brainstem encephalitis24                                                                                                                                          | Breast and gynecological (uterus, ovary, fallopian tube) cancer,3,24,12,30,37,79 NSCLC,16,30 NSCLC,26,31 digestive system cancer,79-96 prostate cancer,30 pleural cancer,83 |
| Anti-Hu             | LEMS, PCD,10,16 PLE, paraneoplastic encephalomyelitis, myelitis, neuronopathy, autonomic dysfunction,1,3 opsoclonus myoclonus syndrome84 | SCLC,15,24,29,34 NSCLC,20 prostate cancer,95 head and neck cancer,96 spindle cell carcinoma,10,20 intestinal cancer,96 |
| Anti-CV2/CRMP5      | PCD,37 paraneoplastic encephalomyelitis, chorea, uveitis, optic neuritis, peripheral neuropathy,1 chronic gastrointestinal pseudo-obstruction, optical neuropathy10 | SCLC,25,96 NSCLC,31 thymoma,30 prostate cancer,95                                                     |
| Anti-Ri             | PCD,23 opsoclonus myoclonus syndrome, brainstem encephalitis, PLE, myelitis,24 neuropathy10                                                                        | Breast and gynecological cancer,24,30,91 SCLC,31                                                     |
| Anti-Ma2            | Paraneoplastic encephalomyelitis, PLE, brainstem encephalitis, PCD1                                                                                                  | NSCLC,1,93 testis cancer7                                                                            |
| Anti-Zic4           | PCD                                                                                                           | SCLC,93,95                                                                                           |
| **Cell-surface ab** |                                                                                                                                                                        |                                                                                                                                                     |
| Anti-VGCCP/Q        | LEMS,7,96 PCD33                                                                                                  | SCLC,29 NSCLC,30,34 MCC96,97                                                                       |
| Anti-Tr             | PCD,34 PLE34                                                                                                     | Hodgkin’s lymphoma,1,2,16,24,29,30 NSCLC (squamous cell lung carcinoma)95                          |
| Anti-mGluR1         | PCD,34 PLE34 PLE34,16 LEMS97                                                                                   | Hodgkin’s lymphoma,1,2,24,96 prostate adenocarcinoma2                                                |
| NSCLC without ab detected |                                                                                                               | 2 patients with squamous-cell lung cancer7,39 16 NSCLC patients without identified tissue type30,36,37 |

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.26 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).1,24,52 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 autoantibodies, 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 autoantibodies.30,36-39 In four patients with NSCLC, squamous-cell lung carcinoma was demonstrated with anti-Tr antibodies in one patient, anti-SOX1 antibodies in one patient, and no identified autoantibodies in the other two patients (Table 1).30,39

**ANTI-SOX1 ABS**

**Demographic characteristics**

This systematic review of 520 cases of patients with anti-SOX1 antibodies included 34 cases without an identified cancer. Among the 284 patients with anti-SOX1 antibodies 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 antibodies and other coexisting autoantibodies, and in 21.2% (n=110) of those with anti-SOX1 antibodies alone. Since the presence of coexisting autoantibodies may also result in the development of clinical symptoms, and hence make it difficult to identify the symptoms attributable specifically to anti-SOX1 antibodies, we analyzed only clinical manifestations in the patients with anti-SOX1 antibodies alone (Table 3).

The neurological presentations of patients with anti-SOX1 antibodies are more diverse than traditionally recognized, and they can be misdiagnosed as neurodegenerative disorders. The neurological dysfunction associated with anti-SOX1 antibodies may involve multiple levels of the neuraxis, including the limbic system, cerebellum, peripheral nervous system, and neuromuscular junction. Among the 110 anti-SOX1 antibody-positive patients with identified cancer, LEMS (30.0%, n=33) was the most common PNS,6,11,12,40-44 followed by PCD (18.2%, n=20),12,16,25,40,44 PLE (18.2%, n=20),6,12,17,40,44 and neuropathy (8.2%, n=9) (Table 3).541-43,46

As the most frequent symptom in patients with anti-SOX1 antibodies, 30.0% of the patients in our review had LEMS and anti-SOX1 antibodies alone. In the literature there are reports of 64% of patients with both LEMS and SCLC presenting with anti-SOX1 antibodies, 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 antibodies patients with unidentified PNS, based on most of them having SCLC.12,48 Therefore, the actual proportion of patients with LEMS and anti-SOX1 antibodies should exceed 30.0%. Our review data support the notion that anti-SOX1 antibodies could be the main predictor of SCLC in patients with LEMS.49

It was intriguing that 78 patients with anti-SOX1 antibodies alone showed no clinical manifestations of PNS. Antineuronal autoantibodies were believed to be immune effectors of neurological dysfunction with regards to membranous antigens (i.e., calcium-channel antibodies). However, anti-SOX1 antibodies are directed against intracellular nuclear proteins, which are subject to a cytotoxic T-cell response.5,50 Therefore, anti-SOX1 antibodies 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 antibody-positive and anti-SOX1 antibody-negative patients in SCLC. Nevertheless, similar to other onconeural autoantibodies (e.g., anti-Hu and anti-Yo), anti-SOX1 antibodies 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 antibodies. The presence of anti-SOX1 antibodies is a potential predictor of underlying SCLC, and SCLC represented the predominant cancer (85.2%, 414 of the 486 cancer patients) (Table 3).6,7,11,12,15,16,21,40-45,51-54 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 antibody-related PNS. Our study found that only 22 patients with anti-SOX1 antibodies 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 polymorph NSCLC (n=1),21 and unspecified NSCLC (n=7) (Table 3).6,12,20 We found that anti-SOX1 antibodies 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 of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|-----------|--------------------------------------------------------|------------------------------------|----------------|---------------------|------------------|---------------|---------------------------------------|------------------|--------------|------------------------------------------|
| Anti-SOX1 abs alone | | | | | | | | | | | |
| Case reports and series | | | | | | | | | | | |
| Sun et al. | 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. | 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. | No underlying cancer during 3-year follow-up | 63/M | Positive | Negative | PCA (chronic), photophobia (subacute) | Diffuse hyperintensities in cerebellum and brainstorm without enhancement | None | 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. | SCLC (1) | 53/M | Positive | NA | Subacute | None | Local excision and IVIg | Chemotherapy | At 3 months, no improvement in PCD |
| Mirallas et al. | 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. | NSCLC (1)[squamous-cell lung cancer] | 76/M | Positive | NA | Acute | None | Chemotherapy and radiotherapy | Mg | Full recovery within 15 days |
| Ge et al. | SCLC (1) Esophagus (1) | 45/M | Positive | NA | Acute | Chronic | Chemotherapy for NSCLC patients | Mg 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 of tumor | Immunotherapy | Outcomes (times from symptom onset) |
|-----------|--------------------------------------------------------|------------------------------------|----------------|-------------------|-----------------|---------------|-----------------------------------|------------------|----------------|-----------------------------------|
| Liu et al.43 | LEMS, neuropathy | SCLC (1) | 72/M | Positive | NA | Subacute | None | None | None | None | Patient abandoned therapy and died 5 months after disease onset |

Research articles

| 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 of tumor | Immunotherapy | Outcomes (times from symptom onset) |
|-----------|--------------------------------------------------------|------------------------------------|----------------|-------------------|-----------------|---------------|-----------------------------------|------------------|----------------|-----------------------------------|
| 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 | 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 Li19 | NA | 10 NSCLC patients: squamous-cell carcinoma (4), adenocarcinoma (6) | NA | Abs identified by immunohistochemistry in biopsy specimens | 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 of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|----------------------------|---------------------------------------------------------|-------------------------------------|-----------------|---------------------|------------------|----------------|--------------------------------------|-------------------|--------------|---------------------------------------|
| 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 6/1/M      | Positive            | NA               | Subacute Chronic | NA                                  | Tumor extirpation for bronchial carcinoid | None           | NA          |
| Horta et al.\(^{64}\)       | NA, mostly lung cancer (22)                            | NA                                  | 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

| 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 of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|----------------------------|---------------------------------------------------------|-------------------------------------|-----------------|---------------------|------------------|----------------|--------------------------------------|-------------------|--------------|---------------------------------------|
| Kunstreich et al.\(^{65}\) | SOX1, POA2 (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, IVlg, 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 |

\(^*\)Range, median, and mean, M = male, F = female
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 of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|-----------|--------------------------------------------------------|--------------------------------------|-----------------|---------------------|------------------|---------------|----------------------------------------|------------------|--------------|---------------------------------------|
| 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_R (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 | Male patients died 11 months after PLE onset. Female patient died with date NA |
| Höftberger et al.53 | SOX1, AMPAR, GABA_R (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_R (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 Mg treatment | All died during 1.75-, 12-, and 1.5-month follow-ups |
| Boronat et al.56 | SOX1, GABA_R, VGKC (1) SOX1, GABA_R, 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 of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|--------------------|--------------------------------------------------------|-------------------------------------|-----------------|---------------------|------------------|-----------------|------------------------------------------|--------------------|---------------|----------------------------------------|
| Dogan et al.       | SOX1, GABA_A (1) PLE with gait difficulties            | NSCLC (1)                           | 74/F            | Positive for both abs | SOX1 (+)         | NA              | Unilateral mediotemporal lesion          | Chemotherapy       | Steroids, azathioprine | Improved memory 6 months later |
| Lai et al.         | 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, Mg | Died from myocardial infarction |
| Dik et al.         | 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 radicles 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.       | SOX1, CV2/CRMP5 (2) Neoparathy (2)                      | NA (2)                              | NA              | Positive for all abs | NA               | NA             | NA                                       | NA                 | NA            | NA                                    |
| Ge et al.          | SOX1, VGCC_m (1) LEMS, neuropathy                       | SCLC (1)                           | 48/F            | Positive for both abs | NA               | Chronic | None                                      | Chemotherapy Mg | Limb weakness partially recovered |
| Ueno et al.        | SOX1, Hu, AChR (1) Autonomic PNS                        | SCLC (1)                           | 65/M            | Positive for both abs | NA               | Chronic | None                                      | Chemotherapy Mg | Autonomic symptoms disappeared. Patient still alive 10 months later |
| Zhang et al.       | 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 |
| Graus et al.       | SOX1, VGCC_m (5) PCD                                     | SCLC (5)                            | NA              | Positive for both abs | NA               | NA             | NA                                       | NA                 | NA            | NA                                    |
| 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 of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|-------------------|--------------------------------------------------------|------------------------------------|----------------|-------------------|-----------------|----------------|-------------------------------------|------------------|---------------|----------------------------------------|
| Sabater et al.14   | SOX1, VGCCP/Q, [LEMS (35)]                            | NA                                 | NA             | Positive for both abs | NA              | NA             | NA                                  | NA               | NA            | NA                                     |
|                   | SOX1, Hu (18)                                         | [neuropathy (10), PCD (3), encephalomyelitis (2), PLE (1)] | NA             | NA                | NA              | NA             | NA                                  | NA               | NA            | NA                                     |
| Titulaer et al.14  | SOX1, VGCCP/Q (15); SOX1, Hu (17); SOX1, VGCCl, Hu (13) | SCLC (48)                          | 32–78 (range)* | Positive for all abs | NA              | NA             | 4 patients without chemotherapy    | NA               | Median survival time of 15 months*      |
|                   | LEMS 60% (27), PCD (9), no PNS (18)                   |                                    |                |                   |                 |                |                                     |                  |                                           |
| Hardy-Werbin et al.15 | SOX1, Yo (3); SOX1, Hu (3); SOX1, GAD65 (1); SOX1, Hu, GAD65 (1); SOX1, Hu, Yo, amphiphysin (1) | SCLC (9)                          | NA             | Positive for all abs | NA              | NA             | All patients received chemotherapy  | NA               | NA            | NA                                     |
| Sabater et al.16   | SOX1, VGCCP/Q (10); SOX1, Hu (4); SOX1, Zic4 (1); SOX1, VGCCP, Hu (2); SOX1, VGCCl, Hu, Zic4 (1); PCD (18), LEMS (8) | SCLC (18)                          | NA             | Positive for all abs | NA              | NA             | NA                                  | NA               | NA            | NA                                     |
| Titulaer et al.16  | SOX1, VGCCP/Q, [LEMS (59)]                           | SCLC (59)                          | NA             | Positive for both abs | NA              | NA             | NA                                  | NA               | NA            | NA                                     |
| Tschernatsch et al.46 | SOX1, Hu (3)                                       | Neuropathy (3/3)                   | NA             | Positive for both abs | NA              | Subacute (2) | 2 patients received steroids, Mg, azathioprine, 1 patient received plasma exchange | NA               | One patient reported slight improvement after plasma exchange. No improvement in other 2 patients |
| Horta et al.44     | SOX1, VGCCP/Q, VGCCl, O2/CRMP5 (1); SOX1, VGCCl, VGCCo, Hu (11); SOX1, VGCCl, VGCC (5); SOX1, VGCCl (6); SOX1, VGCC (3); SOX1, Hu (1) | NA                                 | NA             | Positive for both abs | NA              | Chronic (1) | One patient received plasma exchange | NA               | NA            | NA                                     |

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

| Reference | Associated cancer (number of cases) | Age (years)/sex | Serum anti-SOX1 abs | CSF anti-SOX1 abs | MRI FLAIR/T2-weighted increased signal | Disease course | Treatment of tumor | Immunotherapy | Outcomes (times are from symptom onset) |
|-----------|-------------------------------------|-----------------|---------------------|-------------------|----------------------------------------|---------------|-------------------|--------------|-------------------------------------|
| Zekeridou et al.49 | SOX1, VGCC (2) | SC1C (2) | NA | NA | NA | NA | NA | NA | NA |
| Vural et al.47 | SOX1, Zic2 (8) No PNS (8) | SC1C (8) | 55 (mean), Positive for all abs 8×F | NA | NA | NA | NA | All patients received chemotherapy and radiotherapy | None | Median survival time of 26 months |
| Jeffery et al.60 | SOX1, GABA (1) PLE (1) | SC1C (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 (8); SOX1, amphiphysin (1); SOX1, CV2/CMP5 (1); SOX1, Hu, CV2/CMP5 (1) PCD (2), neuropathy (3), encephalomyelitis (3), brainstem encephalitis (1), PLE (1) | SC1C (4) NSCLC (2) (polymorphic and undifferentiated neuroendocrine) | 47–70 (range), Positive for all abs 4×F, 2×F | 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 temporal mesial and hippocampal abnormality; other 2 patients with brainstem encephalitis, neuropathy, and encephalomyelitis showed no abnormality | NA | Median survival time of 38.5 months (range 25–155 months). Clinical outcome NA |

No cancer Graus et al. (2/41),65 Berger et al. (10/18),66 Ruiz-Garcia et al. (2/71),67 Titulaer et al. (2/72),68 Titulaer et al. (6/65),69 Stich et al. (2/8),70 Dogan Onugoren et al. (2/3),71 Tschernatsch et al. (4/9),72 Sabater et al. (1/62),73 Saray et al. (2/2),74 Alessandro et al. (1/1)75

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: 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, 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.
Abnormal DNA methylation of the promoter region of SOX1 is a potential pathogenesis. Notably, a small group (n=34, 6.5%) of the 520 patients with anti-SOX1 abs developed neurological symptoms without underlying tumors, 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. 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. 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. Additionally, 28% of 85 SCLC patients compared with 18% of 210 NSCLC patients had more than 1 ab. In the current review, 245 (47.1%) of the 520 patients showed the coexistence of multi-

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=110) | |
| LEMS* | 33 (30.0) |
| PCD | 20 (18.2) |
| PLE | 20 (18.2) |
| Neuropathy | 9 (8.2) |
| Unidentified | 34 (30.9) |
| Without PNS (n=78) | |
| 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_{Ca} | 157 (86.3) |
| VGCC_{Na} | 10 (5.5) |

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

| Variable | n (%) |
|----------|-------|
| GABA\(\gamma\)R | 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 and the Dutch and Spanish databases. There were 110 patients with anti-SOX1 abs alone and a total of 116 PNS patients due to coexisting PNS in some patients. AMPAR: \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CRMP5: collapsin response-mediator protein-5, CSF: cerebrospinal fluid, GABA\(\gamma\)R: \(\gamma\)-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, VGCC: voltage-gated calcium channel, VGKC: voltage-gated potassium channel, Zic: zinc-finger protein.
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 anti-

gen-specific intrathecal humoral immune responses and the presence of symptoms, supporting the hypothesis of autoimmunity being involved in the pathogenesis. In contrast, PNS associated with onconeural autoabs such as anti-SOX1 abs is mediated by cytotoxic T-cell mechanisms. In addition, a previous study analyzed 489 patients with a clinical suspicion of PNS for the presence of well-characterized onconeural abs. 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. Paired CSF and serum samples were available for only 17 patients with SOX1 reactivity. Among them, 4 patients were negative for anti-SOX1 abs in the CSF, while the other 13 patients showed positive anti-SOX1 abs reactivity in the CSF.

**Neuroimaging features**

According to the commonly accepted diagnostic criteria of PCD from the Euronetwork in 2004, 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, although there have also been reports of diffuse cerebellar enlargement. At present, the consensus is that most PCD patients do not have abnormal cerebellar signals on MRI, and some [18F]fluoro-deoxyglucose positron-emission tomography (18F-FDG PET) findings have revealed the manifestation of cerebellar hypermetabolism in the early stage of PCD. 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 showing normal findings regardless of the follow-up time. Abnormal cerebellar changes were observed in only 3 of the 30 patients with anti-SOX1 abs: 2 patients with PCD had cerebellar atrophy and 1 patient with PCD had diffuse hyperintense lesions in T2-weighted imaging of the cerebellum and brainstem.
In general, 46.7% of the patients \((n=14)\) showed brain lesions, with 11 patients having PLE and 3 having PCD. In addition, 10.0% of the patients \((n=3)\) had spinal lesions. Among all patients with abnormal lesions, one showed both brain and spinal lesions, and only three patients had anti-SOX abs alone; 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.

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. The neurological symptoms did not improve in 10 patients. Among the other patients with or without treatment, 14 died during a follow-up of up to 30.75 months, all of whom were SCLC patients.

PNS is often therapy-refractory and relentlessly progressive. From the perspective of PCD, most patients have a generally poor clinical prognosis. Anti-neoplasms and immunotherapies provide no benefit to most patients, and no more than 10% of patients with PCD are thought to respond to immunotherapy following removal of the neoplasms. This is likely to reflect the early and irreversible destruction of Purkinje cells. However, Mitoma et al. 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. 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, 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. 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.

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.
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**

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**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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**REFERENCES**

1. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. *Lancet Neurol* 2008;7:327-340.

2. Iorio R, Smith PS. Paraneoplastic cerebellar degeneration. In: Gruol DL, Koibuchi N, Manto M, Molinari M, Schmaermann 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 Eurronetwork 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 Neurol Immunol* 2005;165:166-171.

7. Sabater L, Titulaer M, Saiz A, Verschueren J, Gue F, 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, Episkopov 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. SOX1 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-Garcia R, Martinez-Hernandez E, Garcia-Ormaechea M, Espin-Regio 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. Gure AO, Stockert E, Scanlan MJ, Keresztes RS, Jager 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, Arpi 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, Hofbberger 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, Rathbudi R, Raisiah C, Bauer 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, Raisiah C, Volz 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. Hadjiavassiliou M. Immune-mediated acquired ataxias. *Handb Clin Neurol* 2012;103:189-199.

24. Shams’ili S, Greffens 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, Englund T, Bath P, Sottile V. Expression of Sox1, Sox2 and Sox9 is maintained in adult human cerebellar cortex. *J Neurol Neurosurg Psychiatry* 2002;73:1409-1418.

27. Halve S, Isenmann S, et al. Limbic encephalitis due to GABAB and AMPA receptor antibodies: a case series. *J Neurol Neurosurg Psychiatry* 2012;83:326-331.

28. Venkatraman A, Opal P. Paraneoplastic cerebellar degeneration with anti-Yo antibodies—a review. *Neurohospitalist* 2019;9:165-168.

29. 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.

30. Hasadsri L, Huemer F, Melchardt T, Tran K, Neureiter D, Moser G, et al. Tumour Biol 2015;36:4603-4610.

31. Hasadsri L, Lee J, Wang BH, Yekkiran 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. Hauser M, Ferrarini M,通过preference for anti-SOX1 antibodies and paraneoplastic cerebellar deg-
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. Neurosurg Neurol 2020;41:1277-1279.
35. Bruijlan K, Crols R, Humbel RL, Appel B, De Deyn PP. Probably anti-ti-Tr associated paraneoplastic cerebellar degeneration as initial presentation of a squamous cell carcinoma of the lung. Clin Neurosurg Neurol Psych3 2006;10:415-417.
36. Sabater L, Bataller I, Carpenter AF, Aguirre-Cruz ML, Aguirre-Cruz ML, Carpentier AF, et al. Paraneoplastic cerebellar degeneration and non-small-cell lung cancer. J Neurol Neurosurg Psychiatry 2006;77:1359-1362.
37. Hiasa Y, Kunitişi M, Mitsui T, Kondo S, Kuriwaka R, Shigekiyô 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, Tsai 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, Martin-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 Apoptosis 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. Tschernebach M, Singh P, Gross O, Gérretis T, Knevel F, Probst C, et al. Anti-SOX1 antibodies in patients with paraneoplastic and non-paraneoplastic neuropathy. J Neuromuscul Dent 2010;226:177-180.
47. Vural B, Chen LC, Saip P, Chen YT, Ustuner Z, Gonen M, et al. Complicated paraneoplastic neurological syndromes: a report of 22 patients. Neurosurg Clin Neurol 2009;21:393-400.
48. Zekriouda A, Majed M, Hilliopoulos I, Lennon VA. Paraneoplastic autoimmunity and small-cell lung cancer: neurological and serological accompaniments. Thorac Cancer 2019;10:1001-1004.
49. Titulara MJ, Maddison P, Sont JK, Wirtz PW, Hilton-Jones D, Kloosterc 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. Z occultara M, Gastald 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, Giotto B, Vincent A, Graus F. Paraneoplastic limbic encephalitis associated with potassium channel antibodies: value of anti-glial nuclear antibodies in identifying the tu-
mour. 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, Różaś A, Hegedüs 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 paraneoplastic small cell lung cancer. Neurol India 2017;65:1127-1128.
56. Boronat A, Sabater L, Saiz A, Dalmaj I, 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 after synaptic receptor location. Ann Neurol 2009;65:424-434.
58. Ueno T, Hasegawa Y, Hagihara R, Kon T, Nunomura II, Tomiyama M. Integrated treatment for autonomic paraneoplastic syndrome improves performance status in a patient with small cell lung carcinoma: a case report. BMC Neurol 2018;18:189.
59. Zhang YT, Li R, Liu ZH, Dong HQ. [A case of cancerous Lambert Eaton syndrome with SOX1 antibody positive.] J Neurol Ment Health 2016;17:735-737.
60. Jeffery OL, Lennon VA, Pittouk 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, Mögic C, Golombek BS, Schulte-Mecklenbeck A, Wiendi 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, Kantic M, Wiemel 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, Worachot su Lytrakun V, Utipongsaatorn K, Sonpee C, Hemachudha T. Differences and diversity of autoimmunity 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, Ak tas 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, Pittouk SJ, Flanagan EP, Schmeling JE, et al. Autoimmune CRMP5 neuropathy phenotype and outcome defined from 105 cases. Neurology 2018;90:e110-e110.
67. Chen DS, Mallman I. Oncology meets immunology: the cancer-immunity cycle. Immunology 2013;39:1-10.
68. McKeon A, Pittouk SJ. Paraneoplastic encephalomyelopathies: patho-
logy and mechanisms. Acta Neuropathol 2011;122:381-400.
69. Gravetos I, Cavalcante WCP, Castro LHM, Ninamari R, Simabukuro MM. Updates in the Diagnosis and Treatment of Paraneoplastic Neurologic Syndromes. Curr Oncol Rep 2018;20:92.
70. Corsini E, Gaviani P, Ciarchipari L, Lazzaroni M, Ciussi 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, Dalmaj I, Giotto 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-

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nings 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;14:57-58.
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, Voigtlander T, Grisold W. Deterioration of anti-Yo-associated paraneoplastic cerebellar degeneration in a man with adenocarcinoma of the gastroesophageal junction. Dig Surg 2007;24:395-397.
79. 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.
80. 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.
81. Matschke J, Kromminga A, Erbersdobler A, Lamszus K, Anders S, Sulter GA, et al. Anti-Yo antibodies in paraneoplastic cerebellar degeneration in a man with prostatic adenocarcinoma. J Neurol Neurosurg Psychiatry 2007;78:775-777.
82. 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. Ips J Clin Oncol 2013;43:563-568.
83. Mirouse A, Gobert D, Chanouard 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.
84. Storstein A, Rospotnik 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.
85. Tsukamoto T, Mochizuki R, Mochizuki H, Noguchi M, Kayama H, Hiwataishi 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.
86. 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.
87. Honnorat J, Cartalat-Cared 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.
88. Aliprandi A, Terruzzi A, Rigamonti A, Bazzigaluppi E, Tremolizzo L, Ferrarrese C, et al. Paraneoplastic cerebellar degeneration with anti-CV2/CRMP5 antibodies and prostate adenocarcinoma. Neurosci Lett 2015;610:1501-1503.
89. Brieva-Ruiz 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.
90. Bazine A, Fetohi M, Berri MA, Oufroukh 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.
91. 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.
92. Ameneiros-Lago E, Fernández-Fernández FJ, Liñó-Carballeda C. Paraneoplastic cerebellar degeneration associated with anti-Ma2 antibodies. Med Clin (Barc) 2016;147:e55-e56.
93. Bataller L, Wade DF, Graus F, Stacey HD, Dalmaj M. Antibodies to Zic4 in paraneoplastic neurologic disorders and small-cell lung cancer. Neurology 2004;62:778-782.
94. Sabater L, Bataller L, Suárez-Calvet M, Saiz A, Dalmaj M, Graus F. ZIC antibodies in paraneoplastic cerebellar degeneration and small cell lung cancer. J Neuroimmunol 2008;201-202:163-165.
95. Pavoluzzi 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.
96. Zhang C, Emery L, Lancaster E. Paraneoplastic cerebellar degeneration associated with noncutaneous Merkel cell carcinoma. Neurol Neuroimmunol Neuroinflamm 2014;1:e17.
97. Sillives Smitt P, Kinoshita A, De Leeuw B, Moll W, Coemsans M, Jaarsma D, et al. Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. N Engl J Med 2000;342:21-27.
98. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GAB(A) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010;9:67-76.