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Case Report

Paraneoplastic cerebellar degeneration combined with Lambert-Eaton myasthenia gravis syndrome in a patient positive for SOX1 antibody

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Abstract: A paraneoplastic syndrome (PNS) is a complex condition that worsens the quality of life of patients. It presents diverse clinical manifestations and can be challenging to diagnose. The role of the SOX1 antibody in PNS has been gaining attention, but clinicians frequently lack an understanding of PNS cases with positive antibody results and complex symptoms. This lack of understanding can lead to misdiagnosis and missed diagnoses. In this report, we present a typical case to highlight the importance of considering PNS when patients present with cerebellar lesions, symptoms resembling Lambert-Eaton myasthenic syndrome (LEMS), signs of peripheral nerve injury, or subclinical evidence. Recognizing these indicators of PNS is crucial for improving early diagnosis and patient prognosis. By sharing this case, our goal is to increase awareness of these unique PNS cases and provide insight for diagnosis and treatment.

Keywords: Paraneoplastic syndromes, paraneoplastic cerebellar degeneration, Lambert-Eaton myasthenia gravis syndrome, SOX1 antibody, small cell lung cancer

Introduction

Paraneoplastic syndrome (PNS) is a complex group of findings closely associated with malignant tumors. As tumors develop and progress, changes occur in the body's internal environment. Tumors not only proliferate and metastasize from the primary site, but they can also secrete specific products or trigger multisystem lesions through mechanisms that are not fully understood. This disorder of the immune response is particularly prominent in the nervous system, ultimately leading to the development of PNS [1].

It should be emphasized that the clinical manifestations of PNS are not caused by direct compression, invasion, or metastasis of the tumor, as is commonly understood. Instead, they result from an indirect effect mediated by a series of complex pathophysiologic processes triggered by the tumor. Essentially, a PNS is a rare immune-mediated consequence of the interaction between a tumor and the nervous system. The existence of this syndrome has presented significant challenges in clinical diagnosis and treatment, since it involves the interaction of two complex systems and the mechanism has not been fully clarified.

In terms of clinical diagnosis, the detection of specific tumor-associated neuronal antibodies provides an important basis for the diagnosis of Paraneoplastic Neurological Syndrome (PNS).

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However, PNS is not common in clinical practice, and its incidence is only 1%-3% of cancer patients [2]. This low incidence causes many clinicians to have insufficient understanding of it and easily overlook relevant symptoms, thereby delaying diagnosis and treatment. We report this case to raise awareness of the details of PNS-related cases and to improve clinicians' understanding and diagnosis of this disease.

Case presentation

A 64-year-old female patient presented to The Third Central Hospital of Tianjin with complaints of "progressive right limb dyskinesia for 7 months, accompanied by worsening dizziness and dysphagia for 5 months". The patient first experienced weakness in her right leg in October 2020, which gradually made it difficult for her to walk upstairs. In November, she developed weakness in her right upper limb. By December, she also had dizziness and dysphagia which progressively worsened, eventually leading to double vision. The patient was admitted to a local hospital where a cranial (**Figure 1**) + cervical Magnetic Resonance Imaging (MRI) scan revealed mild demyelinating changes in the white matter of the brain and degenerative changes in the cervical spine. The diagnosis given was encephalocele and ischemic cerebrovascular disease. After receiving treatment (specific details unknown), the patient was discharged with no significant improvement. In April 2021, the patient experienced intermittent episodes of worsening dizziness accompanied by vomiting. However, a subsequent cranial CT scan did not reveal any abnormalities. She was once again diagnosed with ischemic cerebrovascular disease and discharged after receiving appropriate treatment. In June 2021, the patient presented to The Third Central Hospital of Tianjin with exacerbated mobility of her right limb, as well as increased dizziness and difficulty swallowing (dysphagia). The patient had a history of smoking for over 50 years, averaging 20 cigarettes per day. There was no pertinent family medical history. During the neurological examination, the patient's blood pressure was measured at 130/80 mmHg. She was conscious and alert but had difficulty speaking clearly (dysarthria). Pupils were equal in size bilaterally and there was no ophthalmoplegia. However, the left pupil appeard constricted. The strength of the right masticator muscles was weak, but the other cranial nerves did not show significant abnormalities. The muscle volume in the extremities was normal. The strength of the muscles in the left upper extremity was grade V, whereas the strength in the right upper extremity and both lower extremities was grade V-. Muscle tone in the extremities was normal. Tendon reflexes in both upper extremities were brisk (++), and were present in both lower extremities (+). The bilateral Babinski sign was negative. Ataxia and hyperalgesia were observed in the right limb.

A routine blood test was conducted upon admission, which included tests for blood count, liver and kidney function, immune components, cerebrospinal fluid biochemistry, and fasting blood glucose. All results came back normal except for an increase in fibrinogen levels to 5.10 g/L (normal range: <4 g/L). Thus, this patient was an elderly female with a history of heavy smoking for many years and a chronic disease with progressive right limb movement impairment for 7 months, accompanied by dizziness and difficulty swallowing for 5 months. The neurologic examination did not present typical signs of localization, and no abnormalities were found in the cranial MRI. However, the patient exhibited low-frequency decreasing and high-frequency increasing in the neurophysiology tests (**Figure 2**), as well as motor nerve axonal and sensory nerve injury (**Tables 1**-**3**), suggesting the possibility of Peripheral Nervous System (PNS) involvement. Subsequently, the patient underwent additional examinations. The SOX1 antibody test showed positive results in the patient's serum using immunospotting, with a value of 60 AU (where >10 AU is considered positive). However, tests for anti-Hu, anti-Yo, anti-Amphiphysin, anti-CV2, and anti-Ri antibodies yielded negative results. A chest CT scan and immunohistochemistry analysis revealed the presence of small cell lung cancer (SCLC) in the right upper lung (**Figures 3**, **4**). Based on these findings, a diagnosis of PNS was made. The patient was subsequently referred to a specialist hospital, where she received 6 rounds of dovalizumab etoposide immunotherapy and platinum chemotherapy. Following the identification of the etiology and type of pathology, the lesions disappeared, and the patient's neurological symptoms greatly improved.

Discussion

Paraneoplastic neurological syndromes (PNS) are a diverse group of disorders that affect vari-

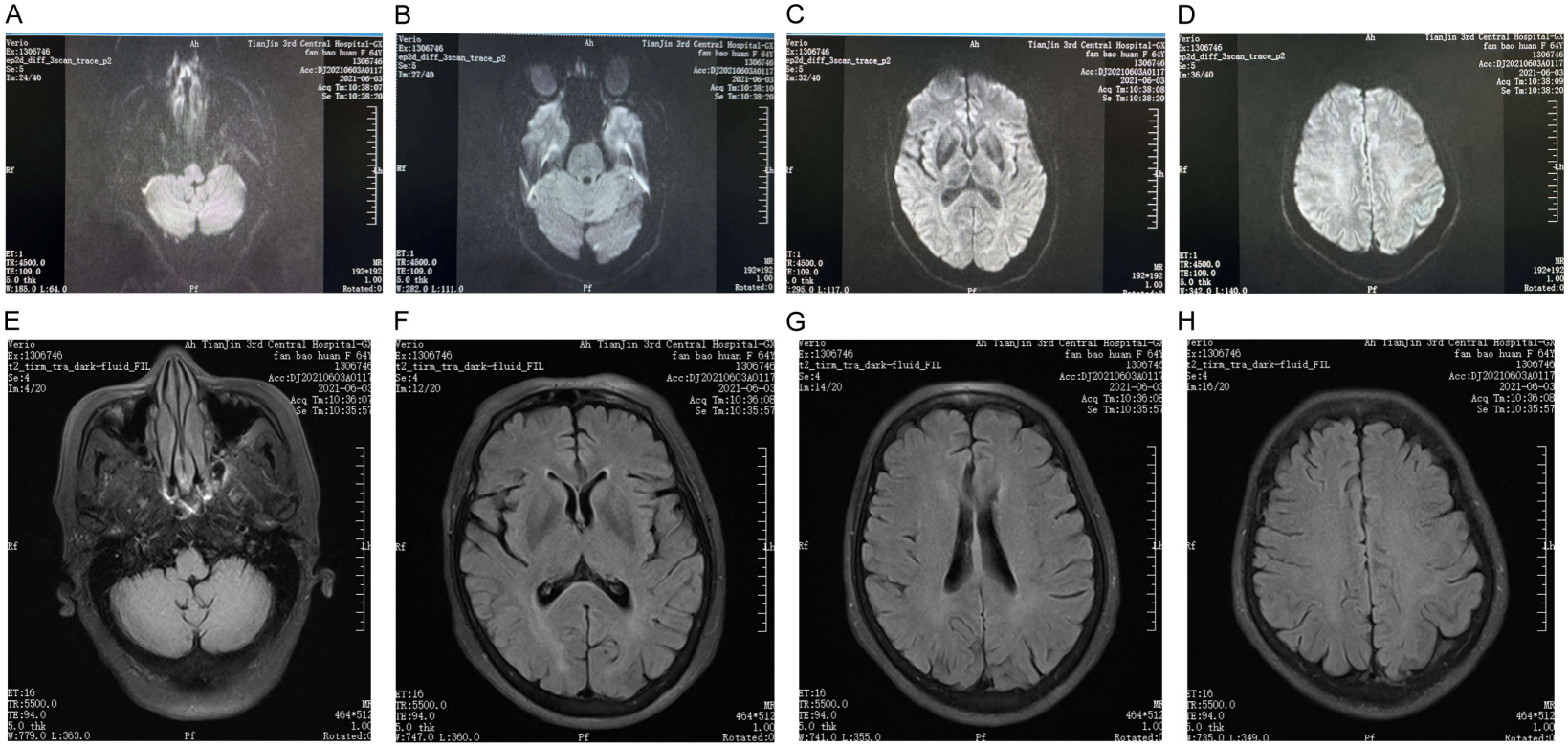

Figure 1. Cranial MRI findings. Mild demyelinating changes in the white matter of the brain. A-D. DWI. E-H. FLAIR.

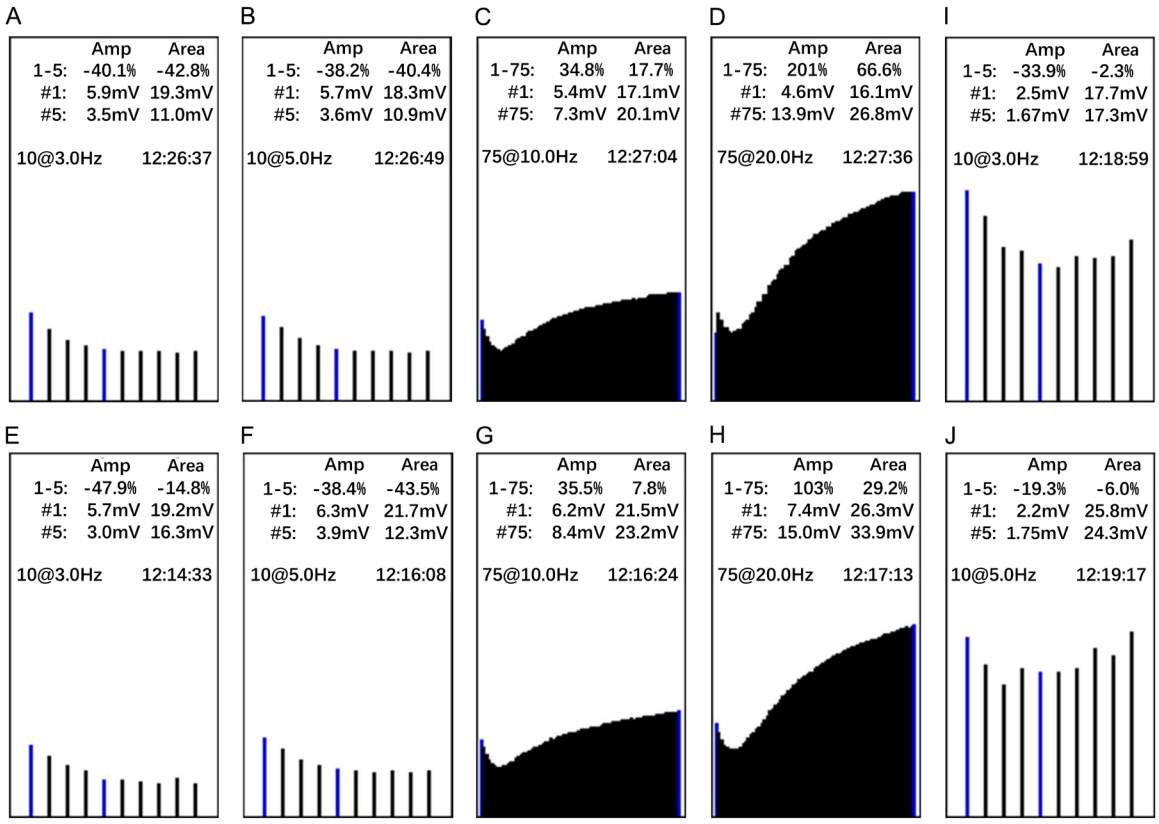

Figure 2. Repetitive electrical nerve stimulation (RNS). A-H. Low-frequency decreasing and High-frequency increasing in the bilateral ulnar nerve. I, J. Low-frequency decreasing in the right axillary nerve.

ous parts of the nervous system, including the central nervous system, peripheral nervous system (specifically motor axons), and neuromuscular junction [1]. The most common form of PNS is paraneoplastic cerebellar degeneration (PCD), which occurs when autoimmune damage primarily affects the cerebellum [3]. PCD is often closely associated with tumors such as lung, breast, and ovarian cancers, and Hodgkin's lymphoma [4]. Classical PCD typically has a subacute course, and patients may present with various symptoms of cerebellar ataxia, such as ataxia, dysarthria, nystagmus, dizziness, and vertigo. Early head-related CT and MRI scans may initially appear normal, except in elderly patients who may show expected cerebellar atrophy [5]. Moreover, the clinical symptoms of PCD often precede the identification of the primary tumor, and approximately 60% of patients develop cerebellar symptoms weeks or months before the tumor is detected, increasing the risk of missing or misdiagnosing the underlying tumor.

In the current case, the patient presented with symptoms such as dizziness, vomiting, and dysarthria. However, cranial imaging examinations did not reveal any abnormalities. These manifestations align with the typical clinical features of PCD, emphasizing the difficulty of accurately diagnosing the condition without clear signs of an associated tumor. This scenario underscores the importance of maintaining a high index of suspicion and conducting a thorough evaluation to prevent misdiagnosis in similar cases.

Antibodies associated with PNS can be categorized into two main groups: intracellular (cancer neuron) targets and cell surface targets [6]. In recent decades, the detection of tumor neuron autoantibodies such as anti-Hu, anti-Yo, anti-collapse response mediator protein-5 (CRMP5), and anti-amphiphiles has improved the diagnosis of PNS [7]. In 2005, Graus identified a novel antibody called anti-glial nucleus antibody (AGNA), in patients with PNS and small cell lung cancer (SCLC). AGNA-positive sera displayed

Table 1. Motor nerve conduction

Nerve	Lat ms	Amp mV	CV m/s
Medianus Motor Left			
Wrist-APB	4.04	3.2↓ %	
Elbow-Wrist	7.77	3.5↓ %	53.6
Medianus Motor Right			
Wrist-APB	4.92↑ %	4.2↓ %	
Elbow-Wrist	8.82	3.8↓ %	55.1
Peroneus Motor Left			
Ankle-EDB	3.09	0.64↓ %	
Bl. Fib. head-Tib. ant	4.28	2.3↓ %	
Fib. head-Ankle	10.8	0.56↓ %	43.5
Peroneus Motor Right			
Ankle-EDB	3.49	0.46↓ %	
Bl. Fib. head-Tib. ant	3.94	2.3↓ %	
Fib. head-Ankle	11.3	0.45↓ %	42.3
Tibialis Motor Left			
Ankle-Abd hal	4.50	5.7	
Tibialis Motor Right			
Ankle-Abd hal	4.38	5.1	
Ulnaris Motor Left			
Wrist-ADM	2.85	3.4↓ %	
Bl. elbow-Wrist	4.18	3.2↓ %	67.7
Ulnaris Motor Right			
Wrist-ADM	2.73	4.4↓ %	
Bl. elbow-Wrist	4.49	4.4↓ %	62.5

The right median nerve had reduced wave amplitude, prolonged latency and normal velocity of motor conduction of; the left median nerve motor conduction had reduced amplitude and normal latency and velocity; the bilateral ulnar and peroneal nerves had reduced wave amplitude. The bilateral posterior tibial nerve had normal motor and sensory conduction.

Table 2. Sensory nerve conduction

Nerve	Peak Lat ms	Amp uV	CV m/s
Medianus Sensory Left			
Dig I-Wrist	2.40	23.6	41.7↓ %
Dig III-Wrist	3.19	12.7	50.8
Medianus Sensory Right			
Dig I-Wrist	2.83	13.6	38.9↓ %
Dig III-Wrist	3.71	9.6	44.5↓ %
Peroneus Sensory Right			
Ankle-fib-head	5.77	1.24	48.5
Tibialis Sensory Right			
Dig I-Med. mal	4.47	1.66	42.5
Ulnaris Sensory Right			
Dig V-Wrist	2.27	15.6	52.9

Slowed sensory conduction in the bilateral median nerve, with normal wave amplitude.

characteristic nuclear staining of Bergmann's glia in the Purkinje cell layer. Furthermore, it was discovered that approximately 43% of LEMS patients with SCLC were seropositive for AGNA, while LEMS patients without cancer tested negative for AGNA [8]. A subsequent study identified SOX1 as the AGNA-compatible antigen. SOX1 antibodies are associated with various clinical manifestations, particularly LEMS and PCD. LEMS is the most commonly observed clinical condition in SOX1 positive patients, followed by PCD. Interestingly, approximately 47.1% of these patients exhibited multiple neuronal autoantibodies simultaneously [7]. Stich suggested that aside from LEMS, SOX1 antibodies may also be present in subacute sensory neuropathy, subacute sensorimotor neuropathy, cerebellar degeneration, brainstem encephalitis, encephalomyelitis, and limbic encephalitis subtypes [9, 10].

In the case of this patient with SOX1 antibody-positive small cell lung cancer, multiple nervous system injuries were observed [11]. The patient primarily presented with PCD symptoms, including limb weakness, dysphagia, and reduced tendon reflexes. Repetitive electrical nerve stimulation (RNS) revealed low-frequency decreasing and high-frequency increasing in the bilateral ulnar nerve, as well as low-frequency decreasing in the right axillary nerve, consistent with LEMS. Motor nerve conduction showed reduced wave amplitude, suggesting bilateral symmetrical axonal damage. Sensory nerve conduction indicated decreased bilateral distal median nerve conduction velocity, with predominant demyelination changes at the site of compression, suggesting carpal tunnel syndrome with a motor over sensory manifestation, consistent with PNS peripheral nerve injury. These findings indicate injuries to the central nervous system, peripheral nervous system motor axons, and neuromuscular junction, as well as two different clinical manifestations of PNS subtypes (PCD, LEMS), and one subtype of subclinical PNS [11].

Several studies have explored immunomodulatory or immunosuppressive treatments for PNS, such as high-dose steroids, intravenous immunoglobulins (IVIgs), plasma exchange, cyclophosphamide, rituximab, sirolimus, or a com-

Table 3. Electromyography of the right anterior tibial muscle suggested neurogenic damage

Muscle	rest	Minimal contraction (MUP)			Maximal contraction (interference phase, mV)
		Mean Amp (uV)	Mean Dur (ms)	% Poly	
Right Abd dig min (man)	--	744	11.9	16.7	mixed phase2.86
Right Abd pollicis brevis	--	932	10.1	11.1	mixed phase2.56
Right Deltoideus post	--	753	12.7	25.0	mixed phase3.06
Right Tibialis anterior	--	2395↑	17.8↑	50.0	simple phase10.3

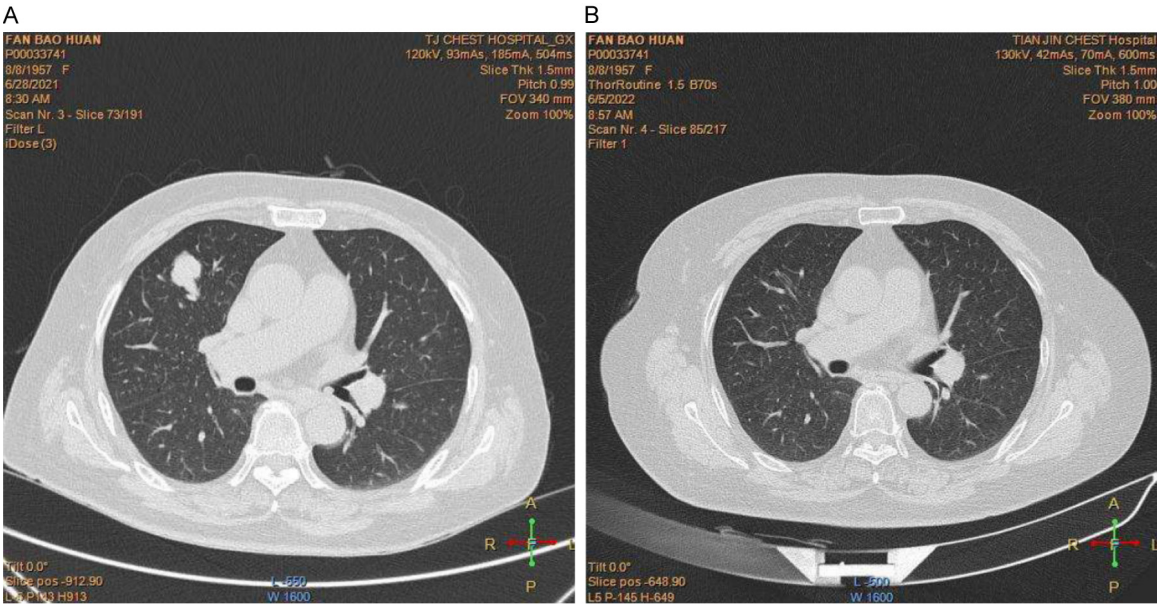

Figure 3. Chest CT findings. A. Space-occupying lesion in the right upper lung (2021. 6. 28). B. Disappearance of right upper lung lesion (2022. 6. 5).

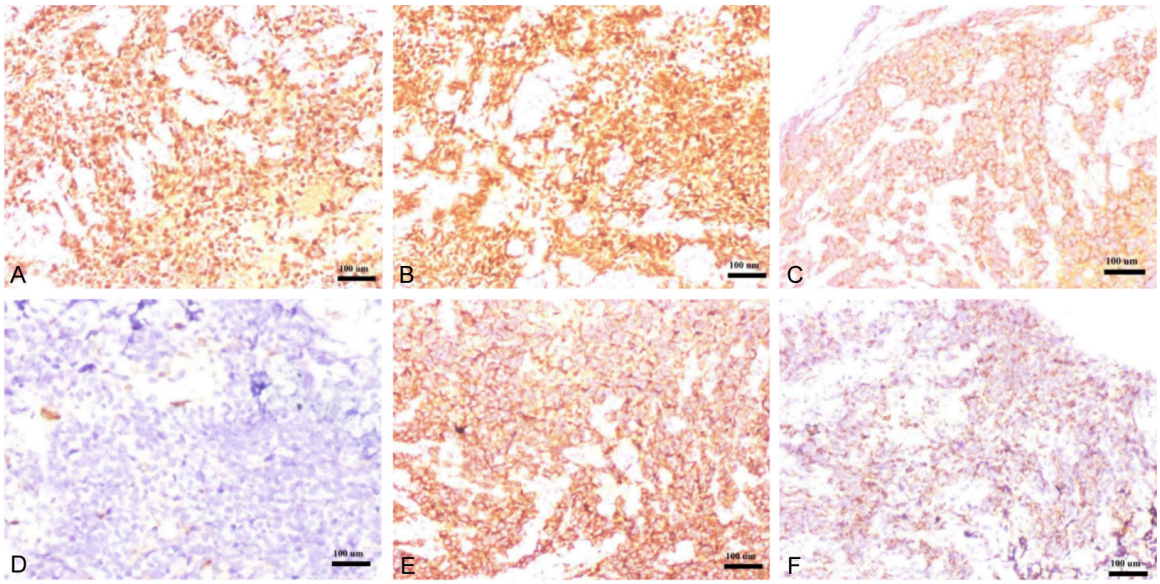

Figure 4. Representative immunostaining of cancer biomarkers in lung tissue. A. Ki67-positive. B. TTF1-positive. C. SYN-positive. D. LCA-positive. E. CD56-positive. F. CK7-positive. Original magnification, 100×.

bination of these therapies [12-17]. While some of these studies have reported slight improvement or rapid progression, overall, their results have been inconclusive and have only provided level IV evidence [18]. A retrospective study of patients with anti-hu antibodies found that early treatment of the tumor was the only factor significantly associated with improvement in neurological disease [19]. The disappearance of the primary tumor lesion with immunotherapy and significant improvement in neurological symptoms observed in this patient lent further support to this finding.

In conclusion, when patients present with symptoms of cerebellar lesions, LEMS, manifest peripheral nerve injury, or subclinical signs, the possibility of PNS should be considered. However, current screening for PNS-related antibodies is often limited to Hu, Yo, Ri, Ma2, and CV26 serum-related antibodies. If these are negative, further screening for the SOX1 antibody is necessary. This additional screening can yield positive results, facilitating further diagnosis, timely detection, and treatment, thereby improving the survival rate and prognosis of patients.

Disclosure of conflict of interest

None.

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