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Clinical characteristics of paraneoplastic neurological syndrome related to different pathological lung cancers

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Abstract

Background: Paraneoplastic syndrome is a distant effect caused by malignant tumors, which is related to the production of cellular immune response. The nervous system is the most common involved system of paraneoplastic syndrome. It is easy to be misdiagnosed. Lung cancer is the most common cancer relating to paraneoplastic neurological syndrome (PNS).

Method: This study retrospectively analyzed clinical data of patients with the combination of PNS and lung cancer between January 2005 and March 2021 at Qilu Hospital of Shandong University, China.

Results: A total of 111 patients were diagnosed with lung cancer complicated with PNS. A total of 95 (85.6%) cases had neurological symptoms as the first symptom. Sixty-three cases had the pathological results. A total of 43 (68.3%) of small cell lung cancer (SCLC) were diagnosed. PNS patients diagnosed with SCLC included peripheral neuropathy (15 cases, 34.9%). PNS patients diagnosed with non-small cell lung cancer (NSCLC) included peripheral neuropathy (6 cases, 30%) and limbic encephalitis (6 cases, 30%). Anti-Hu is popular in patients with SCLC (12 cases, 42.9%) and NSCLC (6 cases, 40%).

Conclusions: Most patients with PNS had neurological symptoms as the first symptom. It was more common in males. It had a higher incidence in SCLC. Peripheral neuropathy was the most common PNS associated with SCLC, followed by Lambert-Eaton syndrome. Peripheral neuropathy and limbic encephalitis were the most common PNS associated with NSCLC. Anti-Hu is the most common antibodies both in SCLC and NSCLC. Tumor markers do not have significant difference between different pathological types.

KEYWORDS
lung cancer, non-small cell lung cancer, paraneoplastic neurological syndrome, small cell lung cancer

INTRODUCTION

Paraneoplastic syndrome is a remote effect caused by malignant tumors, which has nothing to do with the invasion and metastasis of the tumor itself. It is proved that it is related to the production of antibodies mediated by tumor cells because of the cellular immune response.[1] The nervous system is involved in paraneoplastic neurological syndrome (PNS), with a wide range of affected sites and complex clinical manifestations. It is easy to be misdiagnosed. Lung cancer is the most common cancer related to PNS, especially small cell lung cancer (SCLC).[2] PNS occurs in 3%–5% of SCLC.[3] A total of 50%–80% of patients had PNS symptoms and signs before diagnosis of the primary tumor.[4]

There are few studies on the characteristics of PNS caused by different pathological types. This study analyzed the characteristics of PNS of different pathological types to help recognize warning symptoms, make clear diagnosis earlier and provide more targeted treatment.

Aijun Wang is co-first author.

METHODS

This retrospective study initially involved 111 patients with lung cancer combined with PNS between January 2005 and March 2021. Sixty-three patients were confirmed by biopsy or surgical pathology. All patients were excluded from tumor metastasis, oppression, and other diseases that might cause neurological symptoms. The diagnostic criterion of this study refers to the international common diagnostic criteria.[5,6]

Clinical data of all patients were collected. Demographic characteristics, primary diseases, and neurological symptoms were summarized and analyzed retrospectively. The diagnosis and classification of lung cancer were determined according to the pathological examination. Tumor staging depends on surgical pathology, which mainly relies on bronchoscopy, endobronchial ultrasound-guided transbronchial needle aspiration, chest computed tomography (CT), and positron emission tomography (PET)-CT.

PNS has many subtypes associated with neurological manifestations, including Lambert-Eaton syndrome, peripheral neuropathy, limbic encephalitis, subacute cerebellar degeneration, brainstem encephalitis, myopathy, and so on. Relevant laboratory tests including neuron-associated antibodies in blood and cerebrospinal fluid, the routine examination of the cerebrospinal cord, and tumor markers tests were collected. Brain magnetic resonance imaging (MRI), electroencephalogram (EEG) and electromyography (EMG) were done as necessary. Treatment and some prognostic features were also recorded. Finally, antibodies were detected by the immunodot test. It is recommended to conduct the experiment at room temperature (18°C–25°C), preparing the sealing liquid using sodium chloride and disodium hydrogen phosphate, wetting the test trip, incubating the samples, cleaning, incubating secondary antibody, adding pre-diluted alkaline phosphatase-labeled sheep anti-human IgG antibody (MT-152, MYBiotech) to each well, placing it in a shaker incubator at room temperature for 30 minutes, and washing the test strip. Through the enzyme-reaction base, we observed whether the antigen region formed visible speckled staining and judged whether antibodies against PNS-associated antigens existed by the depth of the speckled staining in the antigen coating region.

Statistical analysis

Data were summarized as percentages or medians and ranges. A *t*-test was used for measurement data that were consistent with normal distribution. The χ^2 or Fisher exact test was used for counting data, whereas median and interquartile range were used for description and Wilcoxon nonparametric test were used for comparison between groups. p values <0.05 were considered statistically significant. Analyses were performed using SPSS 17.0.

RESULTS

Demographics of the patients

Among the 111 patients with lung cancer complicated with PNS, there were 77 males and 34 females, with an average age of 61.76 ± 9.07 years. It was more common in males. A total of 95 (85.6%) of the cases had neurological symptoms as the first set of symptoms. A total of 63 patients were diagnosed as definite PNS according to the recommended diagnostic criteria for PNS.[5] Smoking history is significantly more common in patients with SCLC. PNS onset before cancer diagnosis was more noticeable in patients with SCLC (95.3%) compared with patients with non-small cell lung cancer (NSCLC, 60%). Clinical characteristics of the 63 patients are summarized in Table 1.

Distribution of different subtypes among different pathological types

The distribution of different subtypes is illustrated in Table 2. There is no significant difference between the distribution of different subtypes in SCLC and NSCLC ($p > 0.05$). PNS subtypes included peripheral neuropathy (21 cases, 33.3%), Lambert-Eaton syndrome (16 cases, 25.4%), limbic encephalitis (9 cases, 14.3%), subacute cerebellar degeneration (9 cases, 14.3%), myopathy (2 cases, 3.2%), brainstem encephalitis (2 cases, 3.2%), and overlap syndromes (4 cases, 6.3%). Limbic encephalitis was higher in NSCLC compared with SCLC ($p < 0.05$). Details are illustrated in Table 2.

Antibody distribution in different pathological types

Associated antibodies were detected separately in serum and cerebrospinal fluid. The positive antibodies found in cerebrospinal fluid mostly are anti-anti-gamma-aminobutyric acid (GABA) antibodies in patients with limbic encephalitis. Positive antibodies were found in 28 cases (65.1%) with SCLC and 15 cases (75%) with NSCLC. Serum data is illustrated in Table 3. Anti-Hu (42.9% vs. 40%, $p > 0.05$) had a weak increased tendency in SCLC. Anti-GABA was more common in NCLC (33.3% vs. 21.4%, $p > 0.05$). Overlap antibodies included anti-Hu were mostly combined.

Tumor marker characteristics

Tumor markers sometimes could give some clues to the diagnosis of the disease. NSCLC associated antigen and squamous lung cancer associated antigens are the most commonly used tumor antigens. There is no difference between the NSCLC associated antigen (25.6% vs. 25%, $p > 0.5$) and the squamous lung cancer associated antigen (9.3% vs. 10%, $p > 0.5$) (Table 4).

TABLE 1 Demographics of the 63 patients

	SCLC (case/%)	NSCLC (case/%)	*p*
Number	43	20	
Age (year)	61.5 ± 8.03	60.9 ± 9.37	0.808
Gender			0.568
Male	31/72.1	13/65	
Female	12/27.9	7/35	
Smoking history			0.002
Yes	27/62	4/20	
No	16/37.2	16/80	
Disease stage			0.282
Limited	6/13.9	5/25	
Extensive	37/86.1	15/75	
PNS onset before cancer diagnosis			<0.001
Yes	41/95.3	12/60	
No	2/4.7	8/40	
Time from first symptom to cancer diagnosis (month)	5.2 ± 6.6	7.8 ± 6.2	0.143
Cancer treatment			0.350
Operative	5	1	
Immunoglobulin	17	4	
Chemotherapy	9	5	
Multimodality	2	1	
Abandoning	10	9	

Note: $p < 0.05$: difference is significant.
Abbreviations: NSCLC, non-small-cell lung cancer; PNS, paraneoplastic neurological syndrome; SCLC, small-cell lung cancer.

TABLE 2 Distribution of PNS subtypes among different pathological types

	Pathological types			
PNS subtypes	**SCLC (cases/%)**	**NSCLC (cases/%)**	**χ^2/Fisher**	***p***
Diagnosis			12.101	0.06
Subacute cerebellar degeneration	7/16.3	2/10	–	0.706
Peripheral neuropathy	15/34.9	6/30	1.243	0.265
Lambert-Eaton syndrome	13/30.2	3/15	–	0.232
Limbic encephalitis	3/7	6/30	–	0.023
Myopathy	2/4.7	0/0	–	>0.999
Brainstem encephalitis	0/0	2/10	–	0.097
Overlap syndromes	3/7	1/5	–	>0.999

Note: $p < 0.05$: difference is significant.
Abbreviations: NSCLC, non-small-cell lung cancer; PNS, paraneoplastic neurological syndrome; SCLC, small-cell lung cancer.

Characteristics of EEG, EMG, and cerebrospinal fluid

EEG readings were found to be abnormal mostly in patients with encephalitis, especially limbic encephalitis. Slow waves were the prominent characteristics. Spike waves, shark waves, spike-slow waves and shark-slow waves were common in patients with epilepsy diagnosed encephalitis. EMG readings showed decreased low frequency and increased high frequency in patients with Lambert-Eaton. EMG readings had the characteristics of damaged myelin sheath and axons especially of sensory nerves in patients with peripheral neuropathy. Higher proteins and cells were found in cerebrospinal fluid (CSF) in patients with brainstem encephalitis, limbic encephalitis and peripheral neuropathy. There are no abnormal changes in CSF in patients with subacute cerebellar degeneration.

Treatment and prognosis

After the diagnosis, 19 patients abandoned the study. Six patients had the operation. Twenty-one patients had the immunotherapy. Fourteen patients received the chemotherapy

TABLE 3 Different serum antibodies in different pathological types

	Pathological types			
	SCLC (cases/%)	NSCLC (cases/%)	χ^2/Fisher	*p*
Serum antibodies			0.806	0.668
Anti-Hu	12/42.9	6/40	0.033	0.856
Anti-GABA	6/21.4	5/33.3	0.727	0.394
Others	10/35.7	4/26.7	–	0.735
Anti-Ri	1	1		
Anti-Tr	2	0		
Anti-AMP	1	0		
Anti-Yo	2	1		
Anti-CV2/CRMP5	1	1		
Anti-NMDA	1	0		
Overlap antibodies	2	1		

Note: $p < 0.05$: difference is significant.
Abbreviations: GABA, gama-aminobutyric acid; AMP, amphiphysin; CRMP, collapsing response mediator protein; NMDA, N-methyl-D-Aspartic acid; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

TABLE 4 Characteristics of tumor markers in different types

	Pathological types			
	SCLC (cases/%)	NSCLC (cases/%)	χ^2/Fisher	*p*
NSCLC associated antigen			0.002	0.961
Increased	11/25.6	5/25		
Normal	32/74.4	15/75		
Squamous lung cancer-associated antigen			0.008	0.93
Increased	4/9.3	2/10		
Normal	39/90.7	18/90		

Note: $p < 0.05$: difference is significant.
Abbreviations: NSCLC, non-small-cell lung cancer; SCLC: small-cell lung cancer.

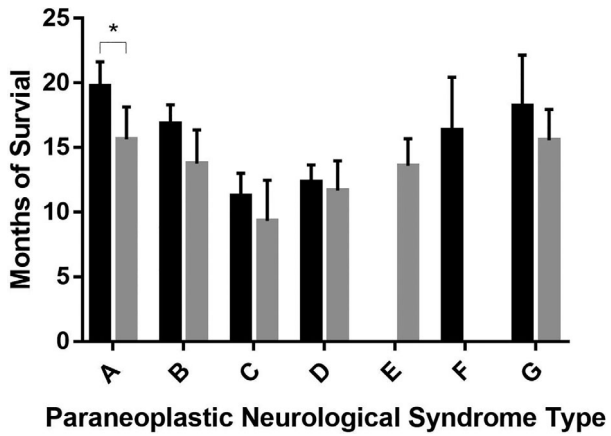

FIGURE 1 Long-term survival in different subtypes. SCLC: small-cell lung cancer. NSCLC: non-small-cell lung cancer. (a) limbic encephalitis; (b) peripheral neuropathy; (c) Lambert-Eaton syndrome, (d) subacute cerebellar degeneration, (e) myopathy, (f) brainstem encephalitis, (g) overlap syndromes. Black bars represent NSCLC, Gray bars represent SCLC

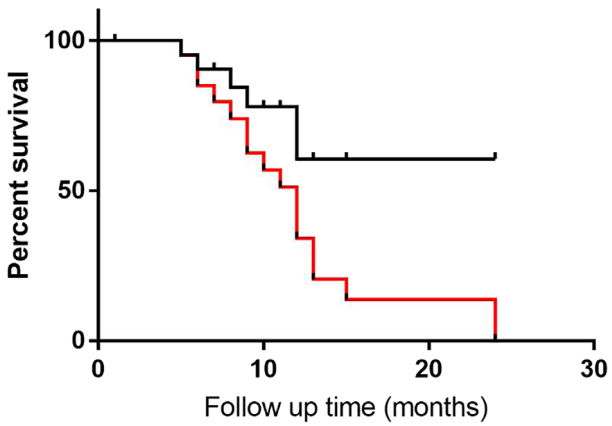

FIGURE 2 Survivorship curve. Survival was significantly higher in the NSCLC group than in the SCLC group ($p < 0.05$). NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer

and radiotherapy. Remission clearly happened in patients who had the operation. Patients with limbic encephalitis responded well to immunotherapy. Other subtypes had partial remission after the use of the immunoglobulin therapy. The survival months were longer in patients with limbic encephalitis happening in NSCLC compared to patients with SCLC ($p < 0.05$). Patients with SCLC tended to have shorter survival times. The differences in the survival times in different subtypes are illustrated in the Figure 1. The survivorship curve in patients with SCLC and NSCLC is shown in Figure 2.

DISCUSSION

PNS is relatively rare, with an incidence of <1% in tumor patients, but it is significantly higher in lung cancer patients, especially those with SCLC, with manifestations of PNS occurring in 3% to 5% of patients with SCLC.[7] Our study retrospectively analyzed the clinical characteristics of patients with lung cancer, including SCLC and NSCLC complicated with PNS.

In our study, it was found that SCLC complicated with PNS mostly occurred in elderly men, and the average age of onset was 61.5 ± 8.03 years, which was similar with NSCLC. Smoking history was more common in patients with SCLC. The nervous system manifestation was earlier than the diagnosis time of lung cancer, accounting for 84.12%, higher than previous reports that 50%–80% of patients showed signs and symptoms of PNS before the diagnosis of the primary tumor.[7,8] The early detection may be due to increased awareness and development of antibody levels in recent years.

The clinical phenotypes of PNS are complex and varied, and neurological symptoms predate the discovery of tumors, making the diagnosis of PNS very difficult. There are some definite PNS subtypes described as follows. Peripheral neuropathy includes subacute sensory neuropathy, acute sensorimotor neuropathy, subacute sensorimotor neuropathy, and chronic sensorimotor neuropathy. We did not differentiate subtypes of this peripheral neuropathy, which perhaps was the reason why it was the most common. Lambert-Eaton syndrome shows clinical manifestations mainly including lower extremity myasthenia. Typical neurological symptoms of limbic encephalitis include varying degrees of short-term memory loss, seizures, and varying degrees of mental disorders. Subacute cerebellar degeneration is mainly characterized by cerebellar ataxia, which includes instability of gait, dysarthria, and nystagmus. Typical symptoms of brainstem encephalitis include ocular motility disorders, diplopia, vertigo, dysphagia, hiccup, etc. Myopathy includes dermatomyositis and acute necrotizing myopathy.

At present, there is no unified diagnostic standard for PNS in China, and the rate of misdiagnosis and missed diagnosis is very high. In our study, the longest time from the onset of neurological symptoms to the discovery of tumor was 4 years. Therefore, even if the tumor is not found immediately after the diagnosis of PNS, long-term follow-up of patients is required. The differences of PNS between SCLC and NSCLC in clinical manifestations, antibody types, and positive rates suggest that there are different potential mechanisms. In our study, it was found that peripheral neuropathy was the most common PNS in patients with SCLC, followed by Lamber-Eaton syndrome. Peripheral neuropathy and limbic encephalitis occurred more often in patients with NSCLC. Anti-Hu was the most common both in SCLC and NSCLC. Other antibodies were more present in SCLC. The advent of antibody testing has provided a great help in diagnosis. Antibodies were divided into antineuronal nuclear antibody (ANNA) by T-cell's immune response and antineuronal surface antibody by B-cell's immune response. ANNAs include anti-Yo, anti-Ri, anti-CV2/CRMP5, anti-amphiphysin (AMP), anti-Ma2, and anti-SOX. Antineuronal surface antibodies include anti-voltage-gated calcium channels and anti-N-methyl-D-aspartic acid receptor antibodies (NMDA). The development of antibodies has greatly improved clinical diagnosis.

Some new reports suggest that SCLC may trigger N-methyl-D-aspartic acid receptor 1(NMDAR1) autoimmunity although the expression of NMDAR1 subunits as onconeural antigens.[9,10] SOX2 antibodies were detectable in 61% of patients with Lambert-Eaton myasthenic syndrome (LEMS)-SCLC, and in other paraneoplastic disorders, such as opsoclonus-myoclonus and paraneoplastic cerebellar degeneration, only when there was an underlying SCLC. SOX2 antibodies are specific (>90%) markers for SCLC.[11,12] However, SOX2 antibodies were not detected in our study. A novel antibody biomarker of neurologic paraneoplastic autoimmunity specific for phosphodiesterase 10A (PDE10A) defines a novel rare neurologic autoimmune syndrome and expands the spectrum of diagnosable paraneoplastic CNS disorders. The intracellular location of PDE10A suggests a T-cell-mediated pathology targeting cells displaying major histocompatibility complex 1-bound PDE10A peptides.[13,14]

Eye-movement recordings in Hu-PNS patients might be a useful tool to objectively monitor progression and treatment efficacy in Hu-PNS patients.[15]

With the development of the therapy, more prominent PNS were induced. Immune checkpoint inhibitors have the potential to worsen pre-existing anti-Hu PNS and may promote the development of anti-Hu PNS in the anti-programmed cell death-1 (PD-1) treatment. One report, including 1304 patients, illustrated anti-PD-1 or anti-PD-L1 immunotherapy could worsen or reveal PNS.[16] In one report, a patient with CV2/ CRMP5-assciated striatal encephalitis was induced by atezolizumab in a case with SCLC.[17]

During the treatment process of the tumor, we should always be alert to the emergence of neurological symptoms. The treatment of primary tumors can be more effective in alleviating the nervous system symptoms than immunotherapy. Candler et al. followed up 63 patients with PNS and found that only the treatment of the primary tumor could significantly improve the prognosis of PNS patients.[18,19] Surgical resection of the tumor was an effective means to treat the primary disease. After tumor resection by biopsy, the nervous system also improved to a certain extent, which might be related to the reduction of tumor antibodies after tumor resection. However, SCLC has special tumor pathological characteristics, and the benefit of surgical treatment remains to be discussed. There are also literature reports that immunotherapy for PNS can stabilize patients' neurological symptoms and improve neurological function defects as soon as possible, and studies have found that PNS with different immune mechanisms and different neurological cases have different responses to immunotherapy. Many

diagnosed patients in our research abandoned the study, which limited number of cases and the conclusions. We observed some phenomena, such as Lambert-Eaton syndrome, had a good response to immunotherapy; subacute cerebellar degeneration responded poorly to immunotherapy; paraneoplastic myelopathy was refractory against immunotherapy, but in some cases, immunotherapy was successful and resulted in long-term survival.[20]

Appropriate and timely treatments including chemotherapy and radiotherapy, at least in Paraneoplastic cerebellar degeneration-LEMS patients in Japan, that actively treatments on any associated cancer could be expected to improve not only life prognosis but also cerebellar ataxia.[21]

Data were collected from patients who were discharged with a diagnosis of paraneoplastic syndrome, with partial omissions for patients who were first admitted with neurological symptoms, but no tumor or antibody was found. The data may be underestimated because of misdiagnosis. All patients should be followed up longer, and more patients and further prospective studies are needed.

CONFLICT OF INTEREST

No authors report any conflict of interest.

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