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Case Report

Paraneoplastic stiff-person syndrome with lung cancer: a case report and literature review

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Abstract: Stiff person syndrome is a rare autoimmune disease of the central nervous system that manifests as stiffness and painful spasms of the trunk axis and lower limb muscles. Benzodiazepines are the first choice for the clinical treatment of the disease. We reported a case of SPS. The patient presented with stiffness and convulsions of lower limbs, weakness after convulsions, falling off easily, abdominal muscle stiffness, and painful spasms lasting for several minutes and alleviating spontaneously. This was caused or aggravated by fatigue or mental stimulation. Left stiffness and weakness of the muscle after relief was present. A chest-enhanced computed tomography scan (CT) suggested two large ground glass nodules in the upper lobe of the left lung. Biopsy pathology indicated the nodules as adenocarcinoma in situ. The patient's symptoms were significantly relieved after treatment with clonazepam and diazepam combined with pregabalin. The clinical manifestations of SPS vary among patients. The symptoms of the disease are mild or severe. Early identification and treatment can improve the prognoses of these patients.

Keywords: Stiff person syndrome (SPS), paraneoplastic syndrome, lung cancer, autoimmune response, anti-GAD65, benzodiazepines

Introduction

Stiff person syndrome (SPS), an autoimmune disease of the central nervous system, is mainly characterized by stiffness and painful spasms of the trunk axis and lower limb muscles with constant fluctuation and aggravation. Existing studies suggest that the main pathogenesis of the disease are related to several aspects including heredity, virus infection, and autoimmune responses. Virus infections cause the body to produce autoimmune responses based on genetic susceptibility. This causes dysfunction in GABA inhibition of the central nervous system and a persistent increase in spinal motor nerve excitability, affecting the body's agonist and antagonist muscles simultaneously. These processes manifest as stiffness and painful spasms of the trunk axis and lower limb muscles, behaving discontinuously and aggravating progressively. In this case report, we describe several characteristics of this disease including the clinical manifestations, results of the auxiliary examinations, diagnosis, and treatment strategies for a patient with SPS and lung cancer. We reviewed the relevant literature on SPS published in recent years.

Case description

A female patient aged 43 years presented to the local hospital with paroxysmal acanthesthesia of the tip of the tongue for more than 10 years accompanied by a lisp in her speech. She was diagnosed with trigeminal neuralgia and showed no improvement after surgery for the symptoms. The pain at the tip of her tongue gradually spread to the whole tongue but without facial numbness, limb weakness, or discomfort. The pain was relieved with carbamazepine and clonazepam prescription. Six months ago, the patient complained of paroxysmal double lower limbs stiffness and convulsive twitch, with abdominal muscle tension and severe body pain. All these symptoms lasted for 3-5 minutes, leading to the inability to walk and aggravation after overworking or mental stimulation. The patient showed autonomic nerve symptoms including pallor, sweating, anxiety,

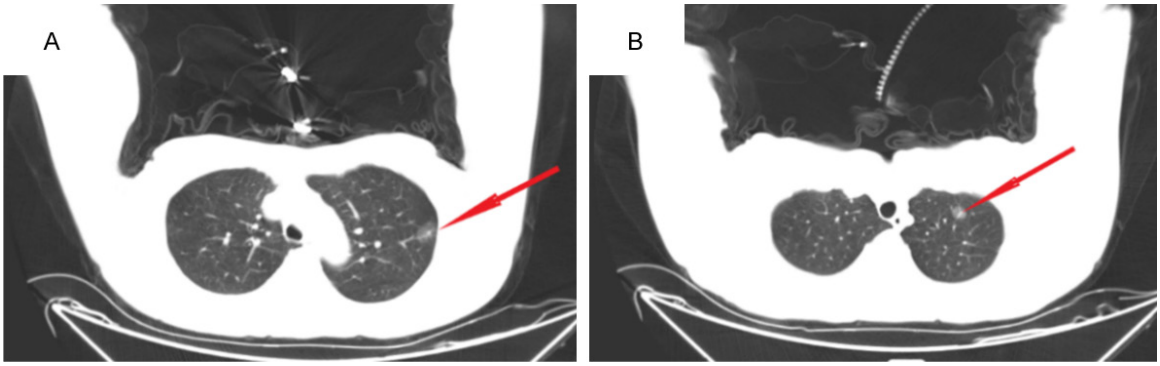

Figure 1. A, B. Chest-enhanced computed tomography scans suggest multiple ground glass nodules in both lungs, and two large ground glass nodules in the upper lobe of the left lung.

and irritability. After relieving the weakness and stiffness in her left lower limb, she would easily fall. In the local hospital, the brain and lumbar MRI (Magnetic resonance imaging) scans showed no obvious abnormalities. She was admitted to our hospital for treatment.

The patient could understand words but could not speak fluently. Both the lower limbs of the patient were stiff and bent, with high muscle tension. The results of other examinations including pupil reflections, eye movements, feeling, muscle strength, and muscle tension of both upper limbs were normal. There were no signs of meningeal irritation. The patient had no history of hypertension, diabetes, heart disease, or thyroid disease. Clonazepam was prescribed to her for many years to control lip pain and was terminated half a year ago. After admission, the patient was treated for improved circulation, nourishing nerves, easing the pain, relieving spasms, and sedation.

Laboratory tests of the patient showed the following: carbohydrate antigen-199 39.46 U/mL (0-39); carbohydrate antigen-125 103.00 U/ml (0-35); urine occultation blood 3+; urine ketone body 2+; positive for antinuclear antibody, titer: 1:320; positive (+) for anti-pm-scl antibody; no obvious abnormalities in the tests for rheumatism, anti-neutrophil cytoplasmic antibodies, thyroid functions, blood routine, blood homocysteine levels, blood coagulation routine, electrolyte test, blood glucose analysis, liver function, and infectious markers. The electromyogram (EMG) when the patient was stable showed no obvious abnormalities (no similar attack occurred after clonazepam was orally administered to the patient following admission). The biochemical, bacterial, and immune indexes of cerebrospinal fluid from lumbar puncture were normal. Cerebrospinal fluid and serum samples were positive for anti-GAD65 IgG levels (58 AU). The patient's tumor markers were relatively high. Digestive tract and ovarian tumors were excluded after completing the relevant examinations including CT and ultrasound scans. The previous lung CT scan of the patient suggested multiple nodules. The re-examination of the chest-enhanced CT scan after admission suggested multiple ground glass nodules in both lungs. Two large ground glass nodules in the upper lobe of the left lung likely indicated pulmonary cancer (**Figure 1**). CT-guided percutaneous lung biopsy was performed to confirm the diagnosis of the patient. Pathological findings indicated that focal alveolar epithelial dysplasia was adenocarcinoma in situ. Combined with the patient's medical history, clinical manifestations, laboratory, and imaging findings, the possibility of withdrawal syndrome caused by the patient's self-withdrawal from clonazepam six months ago was excluded. She was diagnosed with SPS and lung adenocarcinoma.

After the diagnosis was clear, the patient was treated with a combination of clonazepam, diazepam, and pregabalin. Her symptoms were significantly relieved after two weeks, and no similar attack occurred again. The patient was transferred to the thoracic surgery department for surgical treatment after stabilization. The postoperative pathology indicated acinar invasive lung cancer, without involving adjacent lymph nodes or the visceral pleura, and immunohistochemical results suggested positivity

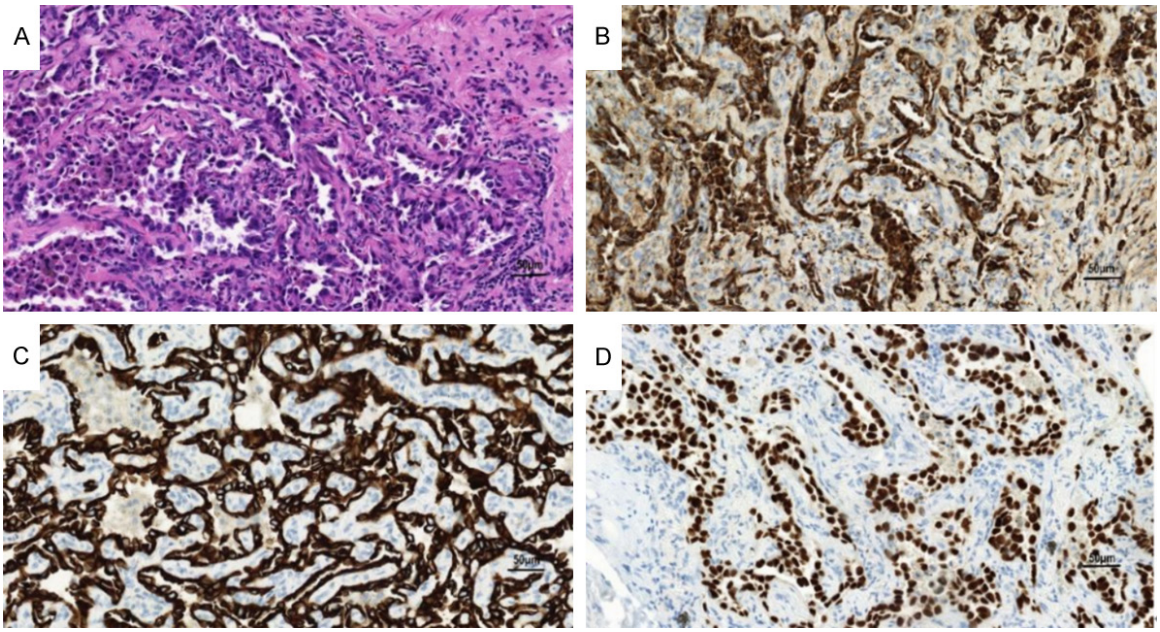

Figure 2. Pathological results and immunohistochemistry (× 400) indicate acinar invasive lung cancer. A. Hematoxylin and eosin stained sections. B. Napsin A (+). C. CK-7 (+). D. TTF-1 (+). Scale Bar = 50 μm.

for napsinA, CK-7, and TTF-1 (**Figure 2**). The patient regularly took the above-mentioned drugs after surgery, and the symptoms did not recur till her subsequent visit half a year later.

Discussion

SPS is an autoimmune disease of the central nervous system and a rare clinical disorder with an incidence of 1-2 per million individuals. The incidence is mostly among young and middle-aged individuals between the ages of 20-50 years, with females being affected more than males with a ratio of 2:1 [1, 2]. This disease was first reported and named by Moersch and Woltlmen in 1956. Related studies have improved and supplemented its clinical characteristics, diagnosis, and treatment. Existing research suggests that the main pathogenesis of the disease are related to several aspects including heredity, virus infection, and autoimmune responses. Virus infections cause the body to produce autoimmune responses based on genetic susceptibility. This causes dysfunction of the GABA inhibition of the central nervous system and persistently enhances spinal motor nerve excitability, affecting the body's agonist and antagonist muscles simultaneously. These processes manifest as stiffness and painful spasms of the trunk axis and lower limb muscles, behaving discontinuously and aggravating progressively [3]. The clinical manifestations of the disease is divided into three types: classic, variant, and paraneoplastic. This disease is often associated with other autoimmune diseases including type 1 diabetes mellitus and autoimmune thyroid disease [4, 5]. Other rare diseases include vitiligo and pernicious anemia [6]. Most patients are positive for autoantibodies. The positivity rate of anti-GAD antibodies in classic SPS can be as high as 60-80%. GADs, specifically GAD65 and GAD67, are the rate-limiting enzymes in the synthesis of γ-aminobutyric acid. Nearly, 80% of the patients are positive for anti-GAD65 antibodies, and 60% are positive for the anti-GAD67 antibody. In this case, the patient showed anti-GAD65 antibody IgG (58 AU) in both serum and cerebrospinal fluid. The anti-GAD antibody is not the only pathogenic antibody. The status of anti-thyroid peroxidase antibody and anti-thyroglobulin antibody can be positive [2, 7]. Nearly 10-20% of patients show complications with tumors, such as lung cancer, breast cancer, and germ cell tumors. The specific mechanism remains unclear but may be related to cross-immune responses. Using "stiff person syndrome" as the retrieval method, a total of 61 cases with complete clinical data between 2000 and 2021 were extracted from the China National Knowledge Infrastructure (CNKI) database. Eleven of these cases had different types

Table 1. Clinical characteristics of patients with stiff person syndrome and cancers

Case	Gender	Age	Symptom	Anti-GAD antibodies	Tumor markers	Concurrent cancers	Treatment	Misdiagnosis history
2015 [18]	Female	48	Stiffness and weakness in the lower limbs	Negative	Negative	Thymoma B1	Benzodiazepines, immune globulin, surgery	(+)
2012 [19]	Male	56	Stiffness and weakness in the lower limbs	Negative	CEA (+)	Thymoma B2	Benzodiazepines, immune globulin, baclofen, surgery	(-)
2021 [20]	Female	71	Pain and stiffness in the left lower limb	Positive	AFP (+)	Liver cancer	Benzodiazepines, pregabalin, baclofen	(+)
2012 [21]	Male	55	Stiffness and weakness in the lower limbs	Negative	Negative	Thymoma B2	Baclofen, surgery	(+)
2012 [21]	Female	22	Stiffness and weakness in the upper limbs	Negative	Negative	Thymoma	immune globulin, surgery	(-)
2012 [21]	Male	48	Stiffness and weakness in the limbs	Negative	Negative	Thymoma	immune globulin, surgery	(-)
2008 [22]	Male	58	Stiffness and weakness in the lower limbs	Negative	Negative	Thymoma B2	Benzodiazepines, baclofen, surgery	(-)
2009 [23]	Male	73	Stiffness in the whole body	-	Negative	Multiple myeloma	Benzodiazepines, glucocorticoid, thalidomide	(-)
2002 [24]	Female	45	Stiffness and weakness in the limbs	Negative	-	breast carcinoma	Benzodiazepines, glucocorticoids, immune globulin, surgery	(-)
2010 [25]	Male	67	Stiffness and weakness in the lower limbs	Positive	CEA (+)	Lung cancer	Benzodiazepines, baclofen, glucocorticoid	(-)
2007 [26]	Male	38	Stiffness in the whole body	Positive	-	Thymoma	Benzodiazepines, glucocorticoid, immune globulins, surgery	(-)

CEA: Carcinoma Embryonic Antigen; AFP: Alpha Fetoprotein.

of cancers, including thymoma, liver cancer, multiple myeloma, breast carcinoma, and lung cancer (**Table 1**). Five undiagnosed patients had elevated tumor markers, including alpha-fetoprotein (AFP), carcinoma embryonic antigen (CEA), and carbohydrate antigen-125. Some reports indicated that patients with paraneoplastic SPS are more likely to be positive for the amphiphysin antibody [2, 8-11].

There is no consensus on the diagnosis of SPS. Referring to Lorish's diagnostic criteria formulated in 1989 and those published by Baizabal-Carvallo and Jankovic in 2015 [12, 13], the diagnosis criteria for SPS is divided into major and minor types. The main diagnostic criteria are: ① muscle stiffness of trunk and limbs, involving abdominal and thoracolumbar paraspinal muscles, which lead to deformities such as lordosis; ② painful muscle spasms, which can be induced by a sudden noise, tactile stimulation, or emotional pressure; ③ EMG showing continuous motor unit potential (MUP) of active and antagonistic muscles, and ④ ruling out neurological diseases or cognitive disorders that explain muscle stiffness. The minor diagnostic criteria include ① positive antibody against glutamic acid decarboxylase 65 (GAD65) or amphiphysin in the serum and ② efficacy of benzodiazepines in treatment. The disease needs to be distinguished from tetanus, forced spondylitis, and congenital myotonia, that can cause forced muscle spasms.

Patients with SPS are sensitive to benzodiazepines. It is the first choice for clinical treatment of the disease [2, 6, 14]. Clonazepam, lorazepam, and diazepam can be selected. These drugs cause inhibitory postsynaptic potential by exciting the GABA receptors, inhibiting the activity of the central nervous system [1, 7]. Crucial drugs for sedation, analgesia, and relieving muscle spasms include: the GABA receptor agonist, baclofen; the neuropathic pain drug, pregabalin; and the sedative drug, midazolam. As SPS is an autoimmune disease of the central nervous system, immune therapy, such as large doses of hormone impact, gamma globulin, and plasma exchange treatment method show good efficacy [3]. An emerging therapy includes the application of the CD20 inhibitor, Rituxan, which has been shown to benefit some patients [6, 7, 15, 16]. For patients with tumors, complete tumor resection before standardized treatment can improve their prognoses. A previous case report introduced an SPS patient with lung adenocarcinoma. The symptoms significantly improved after treatment with clonazepam and surgery [17].

Conclusion

We reported a case of paraneoplastic SPS with lung cancer. We summarized the patient's clinical manifestations, the results of the auxiliary examinations, and the diagnosis and treatment strategies for the disease. The clinical manifestations of SPS vary among patients. The symptoms of the disease are mild or severe and can seriously affect the patient's ability to live. It is expected that the analysis of this case can enhance the early recognition and diagnostic ability of this rare disease in clinical settings. This helps to avoid the delay of early treatment for patients who missed diagnosis or are misdiagnosis.

Disclosure of conflict of interest

None.

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