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CASE REPORT

Case Report: Stiff Person Syndrome with Thymoma

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ABSTRACT —— ***Background.*** Stiff person syndrome is a rare neurological syndrome characterized by fluctuating muscle rigidity and painful spasms. About 5-8% of stiff person syndrome cases are associated with malignant tumors, and the symptoms can manifest as a paraneoplastic disorder. ***Case.*** We herein report a 68-year-old man who was referred to our hospital with a chief complaint of gait disturbance due to painful muscle rigidity in both legs. Examinations of the head and spine showed no abnormalities. However, on chest computed tomography, an anterior mediastinal tumor was seen, and blood tests showed a high titer of anti-glutamic acid decarboxylase antibody. These findings suggested that his symptoms could be attributed to paraneoplastic neurological syndrome associated with the mediastinal tumor. Furthermore, characteristic symptoms and laboratory findings also indicated stiff person syndrome. These symptoms were not affected by initial treatment with steroids, but they were improved by benzodiazepine and baclofen treatment. The pathological diagnosis after radical thymectomy was type B2 thymoma. The patient's postoperative course was uneventful. His medications were decreased, and his symptoms gradually improved. ***Conclusion.*** Thymectomy might offer symptomatic relief for stiff person syndrome associated with thymoma.

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KEY WORDS —— Stiff person syndrome, Thymoma, Paraneoplastic neurological syndrome, Anti-glutamic acid decarboxylase antibody

INTRODUCTION

Stiff person syndrome (SPS) is a rare neurological syndrome that is characterized by fluctuating muscle rigidity and painful spasms. About 5-8% of SPS cases are associated with malignant tumors, and SPS can manifest as a paraneoplastic disorder. A patient with SPS and a thymoma who was treated by a multidisciplinary approach, including thymectomy, with a good outcome is described.

CASE

A 68-year-old man was referred to our hospital with a chief complaint of gait disturbance due to painful muscle rigidity in both legs and an inability to maintain an upright position. His medical history included gastroesophageal reflux disease (personal; no family history). His smoking status was 30 cigarettes per day for 40 years. He was alert, but painful spasms of the upper and lower limbs on both sides rendered standing upright and walking unaided impossible. Symptoms involving the lower extremities were exacerbated by stimuli such as water intake or injections. Magnetic resonance imaging (MRI), cerebrospinal fluid, and laboratory findings including serum tumor markers did not show any abnormalities. Table 1 presents the laboratory findings on admission. Surface electromyography of the right quadriceps muscle and hamstrings at rest showed continuous motor unit activity. Needle electromyography and a peripheral nerve conduction study did not show any abnormal findings. Myelitis was initially suspected and treated with pulse steroid therapy comprising methyl-

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Table 1. Laboratory Findings on Admission

WBC	6.3×10^3/mm^3	TP	6.6 g/dl	CEA	2.4 ng/ml
Neutro	66.3%	ALB	3.9 g/dl	AFP	4.4 ng/ml
Lym	28.2%	AST	17 U/*l*	CA19-9	2.0 U/ml
Mono	5.2%	ALT	21 U/*l*	SCC	0.7 ng/ml
Baso	0.3%	ALP	249 U/*l*	CYFRA	1.7 ng/ml
RBC	3.99×10^3/mm^3	γ-GTP	30 U/*l*	NSE	10.1 ng/ml
Hb	12.0 g/dl	T-BIL	0.5 mg/dl	ProGRP	59 pg/ml
Ht	36.1%	LDH	199 U/*l*	Soluble interleukin-2 receptors	362 U/ml
PLT	330×10^3/mm^3	BUN	12.8 mg/dl	ACE	9.9 U/*l*
		Cre	0.47 mg/dl	Anti-nuclear antibody	
HbA1c (NGSP)	6.8%	eGFR	132 ml/min/1.73 m^2	homogeneous	×40
		UA	3.2 mg/dl	speckled	×40
APTT	31 seconds	Na	141 mEq/*l*	Anti-aquaporin 4 antibody	1.5 U/ml
PT	95%	K	3.8 mEq/*l*	Anti-RNA antibody	5.0 U/ml
Fibrinogen	400 mg/dl	Cl	101 mEq/*l*	Anti-SM antibody	1.0 U/ml
FDP	4.6 μg/dl	Ca	9.3 mEq/*l*	Anti-SS-A/Ro antibody	5.0 U/ml
D-dimer	1.4 μg/dl	CRP	0.05 mg/dl	Anti-cardiolipin antibody	47 U/ml

Underlined cells indicate abnormal values.

ACE, angiotensin-converting enzyme; AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Cre, creatinine; CRP, C-reactive protein; CYFRA, cytokeratin 19 fragment; eGFR, estimated glomerular filtration rate; FDP, fibrinogen degradation products; γ-GTP, gamma-glutamyl transpeptidase; Hb, hemoglobin; HbA1c, hemoglobin A1c; Ht, hematocrit; LDH, lactate dehydrogenase; NGSP, National Glycohemoglobin Standardization Program; NSE, neuron-specific enolase; PLT, platelets; ProGRP, pro-gastrin-releasing peptide; PT, prothrombin time; RBC, red blood cells; RNA, ribonucleic acid; SCC, squamous cell carcinoma antigen; SM, Smith; SS-A/Ro, Sjögren's syndrome A (Ro); T-BIL, total bilirubin; TP, total protein; UA, uric acid; WBC, white blood cells.

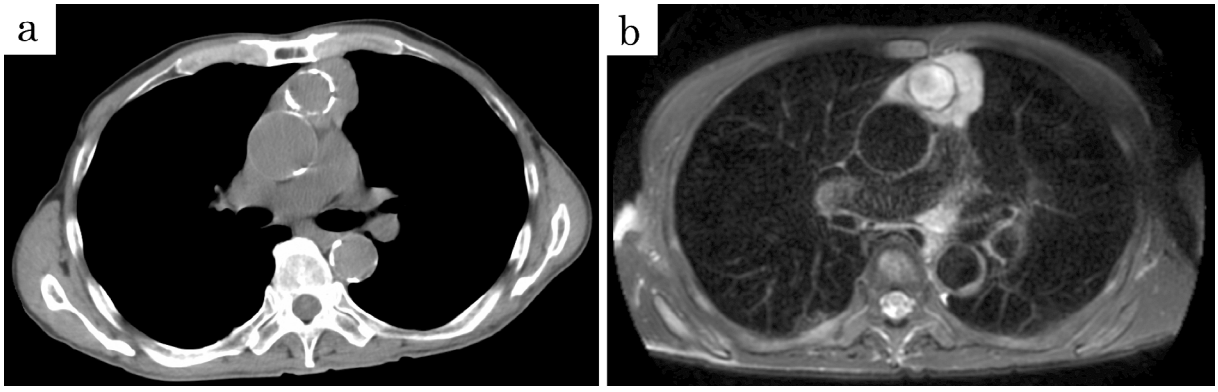

Figure 1. Chest computed tomography (CT) and magnetic resonance imaging (MRI) findings. Anterior mediastinal tumor with a maximal diameter of 50 mm contains ring-shaped calcification **(a)**. T2-weighted MRI shows the tumor as an area of high intensity **(b)**.

prednisolone (1,000 mg/day, three days), but this did not affect his symptoms. Therefore, whole-body examinations were performed. On chest computed tomography (CT), an anterior mediastinal tumor containing an inner ring-shaped calcification was detected. T 2-weighted MRI of the chest also showed the anterior mediastinal tumor as an area of high intensity (Figure 1). Paraneoplastic neurological syndrome (PNS) was suspected, and more detailed blood tests showed a serum anti-glutamic acid decarboxylase (GAD) antibody titer >2,000. These findings suggested that his symptoms were caused by PNS associated with a thymoma. Furthermore, characteristic symptoms and laboratory findings also indicated SPS. Other serum antibodies to acetylcholine receptor,

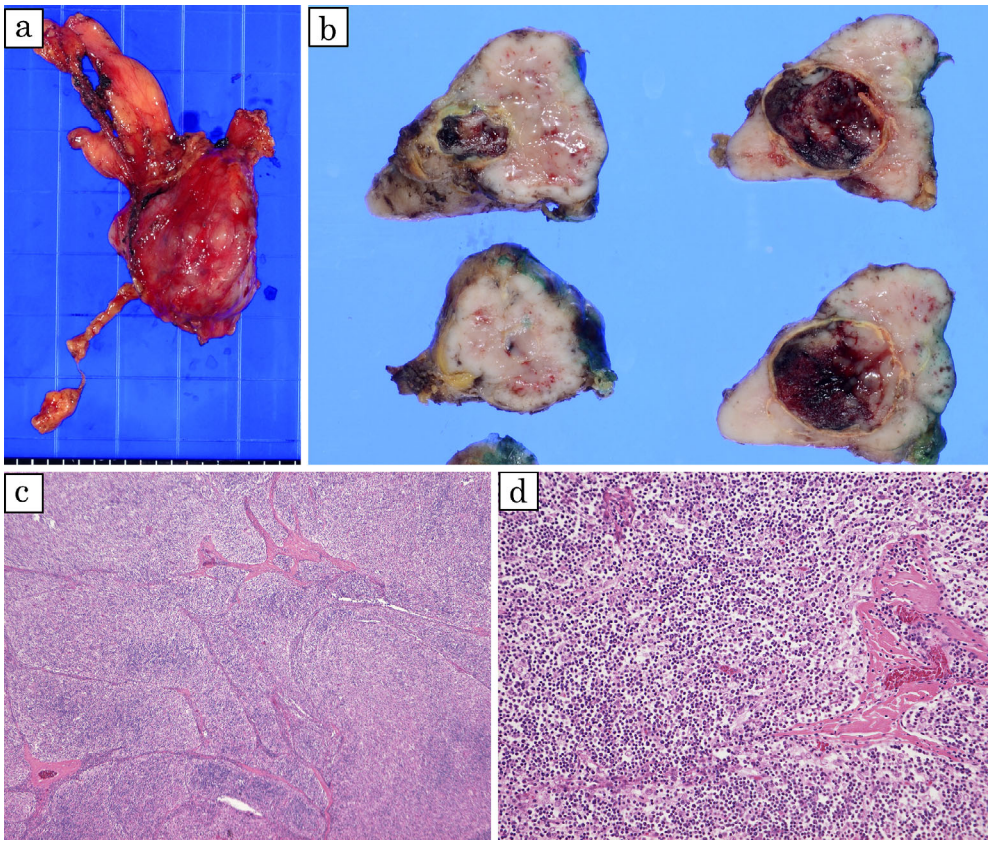

Figure 2. Findings of the resected tumor. The macroscopic gray-white tumor measures 5.8×5.5 cm **(a, b)**. Hematoxylin and eosin staining at low **(c;** ×20) and high **(d;** ×2,000) magnification.

amphiphysin, Yo, Hu, Ri, and CV2 associated with PNS were all negative.

A high titer of serum anti-GAD antibody was detected, and the patient was immediately treated with benzodiazepine and baclofen and then started the following day on a 5-day course of intravenous immunoglobulin (IVIG) therapy (17.5 g/day). His symptoms improved from the first day on this therapy, and he became able to walk using a walker. Thus, the benzodiazepine and baclofen appeared to be effective. The sustained muscle rigidity improved, and the patient was able to walk using the walker, but awareness of intermittent muscle rigidity persisted. Curative surgical resection comprising transsternal radical thymectomy with partial resection of the left parietal pleura due to some tumor invasion was therefore performed.

The size of the gross tumor was 5.8×5.5 cm, with a gray-white, poorly circumscribed, cut surface infiltrated with surrounding mediastinal fat (Figure 2a) and a cystic degenerative component with a calcified capsule at the center (Figure 2b). On microscopy, reticular, proliferative epithelial cells without cellular atypia and abundant lymphocytes were seen (Figure 2c, 2d). The tumor cell nests were surrounded by delicate fibrous septa, and vague intratumorous lymphoid follicles were evident. The tumor was diagnosed as a type B2 thymoma.

The patient's postoperative course was uneventful, and he was transferred on postoperative day 7 to the Department of Neurology to continue treatment for the neurological syndrome. His symptoms gradually improved as his medications were decreased, and he became able to walk with a cane (Figure 3). He was discharged from the hospital approximately one month after surgery. Although the serum anti-GAD antibody titer remained high (>2,000) three months after surgery, follow-up chest CT four months after surgery did not show evidence of recurrent thymoma, and the patient has remained free of relapsing painful muscle rigidity.

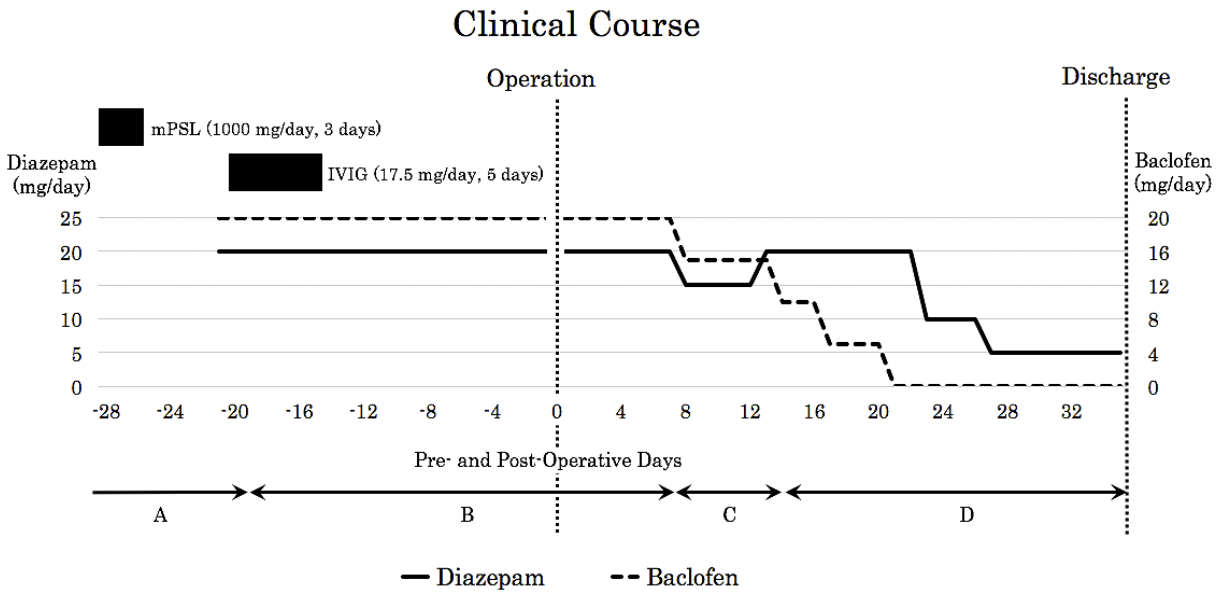

Figure 3. The clinical course of the patient and the transition of symptoms. **A.** The patient was unable to maintain an upright position due to painful muscle rigidity. **B.** Sustained muscle rigidity improved, and the patient was able to walk using a walker. **C.** Muscle rigidity temporarily worsened after diazepam was decreased. **D.** The patient was able to walk using a cane. IVIG, intravenous immunoglobulin; mPSL, methylprednisolone.

DISCUSSION

This patient had neurological symptoms of painful muscle rigidity in both legs exacerbated by stimuli such as water intake or injections. Chest CT and MRI showed an anterior mediastinal tumor that was suspected of being thymoma, and the serum anti-GAD antibody titer was high. Given the above findings, it was considered that SPS had occurred as a PNS associated with the mediastinal tumor.

SPS is a rare neurological syndrome characterized by fluctuating muscle rigidity and painful spasms, and it was first described in 1956 by Moersch and Woltman.[1] The characteristic neurological symptoms are often triggered by stimuli such as psychological factors, sound or conversation, swallowing, and mastication.[2] This syndrome is also known as stiff man syndrome but is now commonly referred to as SPS. An epidemiological survey by McKeon et al.[3] found that 67 of 99 patients with SPS were women, with a median age at symptom onset of 40 years. An autoimmune mechanism is thought to cause SPS. Anti-GAD antibody is positive in about 60% of patients with SPS,[4,5] and this causes gamma-aminobutyric acid (GABA) dysregulation in the brain, which apparently induces the characteristic neurological symptoms. Indeed, GABAergic agonists do reduce symptoms in many patients.[3]

About 5-8% of SPS cases are associated with malignant tumors, and symptoms can resemble those of a paraneoplastic condition.[2,3] The most frequent complicating malignancy is breast cancer, but thyroid, small cell lung, colon, and renal cell carcinomas, as well as lymphoma and thymoma, have also been reported. Antibodies to amphiphysin are frequently detectable under these conditions.[6,7] Several reports have described SPS with thymoma, but this is quite rare, and the frequency is unknown. A summary by Vernino and Lennon found only one patient with thymoma or thymic carcinoma associated with SPS among 201 patients.[8] To our knowledge, only six other patients have undergone thymectomy for SPS with thymoma or thymic carcinoma, and Table 2 summarizes these patients and the present patient.[9-14] They comprised three men and four women, with a median age of 57 (32-79) years old. Six of them were positive for anti-GAD antibody. Although antibodies to amphiphysin are often detected when SPS is associated with malignant tumors,[6] three of these patients were negative for this antibody. The histological subtypes according to the WHO classification were B1 (n=3), B2 (n=2), and others (n=2). Symptoms improved after thymectomy in six of the patients. Three reports describe four cases of recurrence,[9,11,12] and IVIG alone or

Table 2. Literature Review on Thymoma or Thymic Carcinoma Associated with SPS

First author	Demographics		Antibodies		Pathology	Treatment		Outcome
	Age at onset (years)	Sex	GAD	Amphiphysin	WHO	Preoperative treatment	Response to thymectomy	SPS recurrence
Nicholas[9]	55	Male	−	ND	B2	IVIG, GABAergic agonists	Well	+
Hagiwara[10]	40	Female	+	−	B1	Steroids, immunoadsorption	Well	−
Tanaka[11]	57	Female	+	−	B1	GABAergic agonists	Well	+
Iwata[12]	79	Female	+	ND	AB	GABAergic agonists, dantrolene, tizanidine, steroids, IVIG	Well	+
Aghajanzadeh[13]	32	Male	+	ND	C	GABAergic agonists	Well	−
Kobayashi[14]	68	Female	+	ND	B1	−	Poor	
Present report	68	Male	+	−	B2	Steroids, IVIG, GABAergic agonists	Well	−

GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; ND, not described; SPS, stiff person syndrome; WHO, World Health Organization.

combined with GABAergic agonists improved the symptoms in three of these cases. Plasma exchange improved the symptoms in the other patient. Steroids can improve the symptoms when surgery is ineffective. Therefore, a multidisciplinary approach should be considered for such patients. The present patient had no evidence of recurrence at the most recent follow-up, but careful continued follow-up will be required.

The most common subtype of thymoma associated with SPS is type B, which is also associated with myasthenia gravis (MG), usually type B2,[15] supporting the notion that SPS develops via autoimmune mechanisms similar to those associated with MG.

In general, extended thymectomy is the treatment of choice for thymoma associated with MG. This is because thymus tissue in adipose tissue outside the thymus produces antibodies that result in MG. However, whether thymoma or thymic tissue associated with SPS produces anti-GAD antibody is unclear. Therefore, a consensus has not yet been established regarding appropriate surgical procedures or ranges of resection. Although some studies have found that anti-GAD antibody levels decrease after thymectomy,[11,12] non-surgical treatment has been given, and the direct effect of surgery itself is unknown. However, the preoperative dose of medicine can sometimes be reduced without exacerbating symptoms after thymectomy, as was noted in the present patient. Thymectomy may be useful not only from an oncological standpoint but also for symptomatic relief.

The clinical symptoms of SPS can be similar even when anti-GAD antibody is negative or in the absence of malignant tumors or autoimmune diseases. Therefore, a single mechanism might not explain SPS. Further investigations of more patients will be necessary.

CONCLUSION

A patient with SPS and thymoma was described. Thymectomy might be useful for symptomatic relief when SPS is associated with thymoma.

本論文内容に関連する著者の利益相反：なし

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