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Case Report

A Case of Anti-Hu Antibody-positive Paraneoplastic Neurological Syndrome due to Mediastinal Lymph Node Small Cell Carcinoma of Unknown Primary Origin

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Summary

A 65-year-old man visited our hospital with the complaint of rapid exacerbation of dysphagia. He had no otolaryngological or digestive system disorders. He was initially suspected to have acute bulbar palsy, a subtype of Guillain-Barré syndrome, and managed accordingly; however, the patient did not respond to treatment. Subsequently, he developed multiple cranial neuropathies and sensory neuronopathy. Additional tests revealed that he had positive anti-Hu antibodies. No obvious mass lesions were noted, but 3 months later, the patient developed enlarged isolated lymph node near the para-aortic lymph nodes. Excision of the focal lymph node revealed small cell carcinoma, without evidence of small cell carcinoma in the lungs. Therefore, the primary lesion was unknown. The patient was diagnosed with paraneoplastic neurological syndrome. In such cases, tumor search often needs to be repeated because neurological symptoms may precede the tumor onset.

Key Words: anti-Hu antibody-positive paraneoplastic neurological syndrome, small cell carcinoma, unknown primary origin

Introduction

Paraneoplastic neurologic syndrome (PNS) is a rare disease characterized by immunological effects of malignant tumors that lead to various neurological symptoms, such as peripheral neuropathy, dysautonomia, cognitive decline, cerebellar ataxia, neuromuscular junction disorder, seizures, cranial neuropathy, movement disorder, brainstem disorder, and myelopathy[1,2]. Neurological symptoms often precede the appearance of tumors and often no abnormalities are found in the initial tumor search. In such cases, tumor may need to be searched for several years. We report a case of PNS due to small cell carcinoma of the mediastinal lymph

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node with unknown primary origin. The patient developed multiple cranial neuropathies and sensory neuronopathy, which presented as acute bulbar palsy.

Clinical Summary

A 65-year-old man developed discomfort when swallowing from the end of August 2020. After a few days, he was unable to drink water and consulted an otolaryngologist. There were no findings of passage obstruction, so a neurological disease was suspected, and the patient was referred to our hospital. The medical history of the patient was significant for hypertension, gastric ulcer, colon polyp, and cervical spondylosis. He smoked 20 cigarettes a day for 45 years. On admission, he was alert and had dysphagia, diminished pharyngeal muscle reflex, and disappearance of soft palate reflex. No obvious tongue atrophy or fasciculation was observed. Symmetric numbness was observed in the periphery of fingers. The triceps tendon reflex was weak, whereas the others were absent in both upper and lower limbs. Blood thiamine (37 ng/mL; normal range: 24-66), mecobalamin (237 pg/mL; normal range: 180-914), and folic acid (6.4 ng/mL; lower limit: 4.0) levels were in the normal range. ANCA-related autoantibodies, anti-AChR antibody, anti-MuSK antibody, anti-GM1 IgM and IgG antibodies, and anti-GQ1b IgM and IgG antibodies were negative. There was no decrease in the cerebrospinal fluid (CSF)/serum glucose ratio[3] and the IgG index was 0.819 (i.e., slightly elevated)[4]. CSF showed class I cytopathology (Table 1). The head and cervical spine MRI showed no abnormalities. The nerve conduction test showed no decrease in conduction velocity or conduction block. Based on the acute clinical course and laboratory findings, acute bulbar palsy (ABP)[5,6], a subtype of Guillain-Barré syndrome, was suspected and two courses of IVIg were administered. However, the symptoms did not improve. Anti-GT1a antibody, which is a marker of ABP, was negative (Table 2). On the 36th day of hospitalization, right abducens, facial, and hypoglossal nerve palsies appeared, and on the 50th day of hospitalization, he required intubation and mechanical ventilation for respiratory failure. The patient was investigated to rule out malignant lymphoma and PNS as the causes of his symptoms. No abnormal findings were found on random skin biopsy or whole-body CT. We were unable to conduct a PET study at our facility. The laboratory findings showed a slight increase in sIL2R, CEA, and SCC levels. The anti-Hu antibody was positive. Progastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) specific to small cell carcinoma were not elevated initially but became significantly elevated at the later stage (ProGRP: 111 pg/ml). Although no pulmonary lesion was observed on chest CT, progressive enlargement of the lymph node near the para-aortic lymph node was observed at about 3 months (Fig. 1). Lymph node excision was performed at that site using video-assisted thoracic surgery, which led to the diagnosis of PNS associated with small cell carcinoma (Fig. 2). No chemotherapy or radiation therapy was administered after excision and 16 months after the resection, no new lesions were found on chest CT scan. In addition, the patient was alive without exacerbation of his neurological symptoms.

Discussion

PNS is a rare disease that affects less than 0.01% of cancer patients[1]. More than half of the patients have neurological symptoms due to the tumor, and most tumors are diagnosed within 2 years of onset of neurological symptoms. The neural antibodies are detected in less than 50% of patients[2]. The diagnosis is strongly suspected if the treatment of the tumor improves the neurological symptoms. The 2021 diagnostic criteria for PNS-associated antibodies are as follows: high-risk antibodies with more than 70% tumor complications, intermediate-risk antibodies with 30-70% tumor complications, and low-risk antibodies with less than 30% tumor complications (i.e., essential autoimmune diseases)[7]. High-risk antibodies typically present with subacute cerebellar ataxia, limbic encephalitis, encephalomyelitis, and subacute sensory ataxic neuropathy. In our patient, high-risk antibodies (i.e., anti-Hu antibody) presented with ABP, oculomotor palsy, and peripheral neuronopathy.

ABP was initially suspected and treatment was initiated, but the patient did not improve. Subsequently, the patient developed new multiple cranial nerve palsies of late onset, suggesting that the disease course was different than that in ABP. The isolated lymph node near the aortic arch enlarged over time, which led to the diagnosis of the tumor. Hu antigen is found

Table 1 Laboratory Findings at the Admission.

Hematology		TP	7.2 g/dL	*Serology*		*Cerebrospinal fluid*	
WBC	7.1 × 10^9 /L	Albumin	4.28 g/dL	CRP	0.41 mg/dL	Cell	9 /μL (M:P 8:1)
RBC	4.42 × 10^{12} /L	UN	22 mg/dL	FT4	1.10 ng/dL	TP	61.0 mg/dL
Hb	14.3 g/dL	Na	143 mmol/L	FT3	1.00 pg/mL	Glucose	51.1 mg/dL
Ht	42.9 %	K	4.6 mmol/L	TSH	0.828 μU/mL	CSF/serum glucose ratio	0.448
MCV	97.1 fL	Cl	108 mmol/L	IgG	1137.4 mg/dL	Albumin	32.6 mg/dL
MCH	32.4 pg	UA	13.6 mg/dL	**CEA**	**6.1 ng/ml**	IgG	7.1 mg/dL
MCHC	33.30 %	Creatinine	0.89 mg/dL	**SCC**	**6.7 ng/ml**	ADA	< 2.0 U/L
Platelet	23.8 × 10^4 /μL	Glucose	114 mg/dL	ProGRP	36.4 pg/ml	MBP	< 40.0 pg/mL
Coagulation		CPK	60 U/L	NSE	9.0 ng/ml	sIL2R	< 30 U/mL
PT-INR	0.98	HbA1c	5.0 %	**sIL2 receptor**	**1440 U/ml**	**OB**	**positive**
APTT	30.3 sec	TG	102 mg/dL	PR3-ANCA	< 1.0 U/mL	**IgG index**	**0.82**
D-dimer	0.63 μg/mL	HDL-C	45 mg/dL	MPO-ANCA	< 1.0 U/mL	Cytology	class I
Biochemistry		LDL-C	115 mg/dL	CLβ2GP1 Ab	< 1.2 U/mL		
AST	19 U/L	Thiamine	37 ng/mL	ACE	8.4 U/L		
ALT	15 U/L	Mecobalamin	237 pg/mL	ADA	9.2 U/L		
ALP	143 U/L	Folic acid	6.4 ng/mL	Anti-AchR Ab	0.2 nmol/L		
LDH	109 U/L			Anti-MuSK Ab	< 0.01		
GGT	21 U/L			**Anti-Hu Ab**	**3 +**		
T-Bil	1.20 mg/dL						

Abbreviations: ACE, angiotensin converting enzyme; Anti-AchR Ab, anti-acetylcholine receptor antibody; Anti-Hu Ab, antineuronal nuclear antibody; Anti-MuSK Ab, anti-muscle-specific tyrosine kinase; APTT; activated partial thromboplastin time; DA, adenosine deaminase; AST: aspartate aminotransferase, ALT: alanine aminotransferase; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; GGT, γ-glutamyltranspeptidase; Cl, chloride; CPK, creatine phosphokinase; CRP, C-reactive protein; Hb, hemoglobin; HDL-C, high density lipoprotein cholesterol; Ht, hematocrit; K, potassium; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MBP, myeline basic protein; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibodies; Na, sodium; NAG, N-acetyl-β-Dglucosaminidase; NSE, neuronspecific enolarse; OB, Oligoclonal band IgG; Plt, platelet; PR3-ANCA, proteinase-3-anti-neutrophil cytoplasmic antibodies; ProGRP, pro-gastrin releasing peptide; PT-INR, prothrombin time-international normalized ratio; RBC, red blood cell; SCC, squamous cell carcinoma antigen; sIL2 receptor, soluble interleukin 2 receptor; T-Bil, Total Bilirubin; TG, triglyceride; TP, total protein; UA, uric acid. Bold were abnormal findings.

in the nucleus and cytoplasm of neurons in the cerebrum, spinal cord, and dorsal root ganglia; this antigen is believed to be involved in cell development and differentiation.

Anti-Hu antibody positivity is associated with a high rate of SCLC[8]. Although neurological symptoms were observed before the diagnosis of tumor, no pulmonary lesions other than lymphadenopathy were observed during the disease. Several cases of anti-Hu antibody-positive PNS with lymph node metastasis of unknown cause have been reported in Japan[9,10]. Neurologic findings in these patients included abnormal sensations in the upper extremities, diminished tendon reflexes, and normal nerve conduction studies. Our patient had sensory neuronopathy due to positive anti-Hu antibodies. The treatment of PNS begins with the treatment of the causative tumor and early treatment may result in a relatively favorable prognosis for neurological symptoms. Immunotherapy, such as plasma exchange, IVIg, and steroids, is also used for neurological symptoms, but patients with antibody positive against the intracellular antigens, such as anti-Hu antibodies, are generally resistant to immunotherapy[11]. It has also been reported that IVIg is less effective for central nervous system symptoms than for peripheral nervous system symptoms. In the present case, improvement in the tendon reflexes of the upper extremities was observed after IVIg administration, suggesting that IVIg improved the peripheral neuropathy[12]. Syndromes mediated by surface neuronal autoantibodies usually respond to prompt immunotherapy in addition to oncological therapies; some syndromes associated with 'onconeuronal' antibodies may not respond, but there are important exceptions[13].

Table 2 Antiganglioside antibody results in the present case.

	IgM	PA +	IgG	PA +
GM1	-	-	-	-
GM2	-	-	-	-
GD1a	-	-	-	-
GD1b	-	-	-	-
GT1a	-	-	-	-
GT1b	-	-	-	-
GQ1b	-	-	-	-
GD3	-	-	-	-
GalNAc-GD1a	-	-	-	-
Gal-C	-	-	-	-
GA1	-	-	-	-

Results are displayed as the OD value based on the ELISA response. ELISA, enzyme-linked immunosorbent assay; OD, optic density; PA +, complex of glycolipid with phosphatidic acid.

In a study of 686 cases with metastatic cancer of unknown primary site[14], bones, lungs, and liver were the common sites of metastases, whereas adenocarcinoma[15], carcinoma, and anaplastic carcinoma were the most common histological types. Small cell carcinoma was relatively rare and found in only 3 cases (0.4%)[14]. In our patient with isolated para-aortic lymph node carcinoma, the repeated CT scan did not show a new primary lesion. The neurological symptoms persisted, but did not progress and the patient survived. If the metastatic lesion is single station lymph node carcinoma, treatment with excision alone may be sufficient and some patients survive for several years[16,17].

In conclusion, we reported a case of anti-Hu antibody positive PNS as one of the differential diagnoses of subacute progressive ABP. In such patients, various systemic diseases should be promptly excluded, and the tumor search should be repeated.

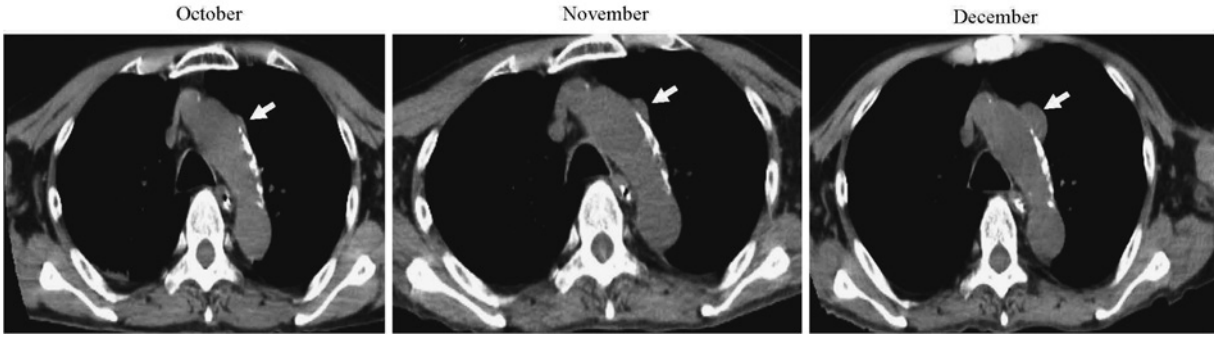

Figure 1

Chest computed tomography showing enlargement of the isolated para-aortic lymph node (white arrow).
Tumor size; October 2020: 3.99 × 9.88 mm; November 2020: 6.79 × 14.76 mm; December 2020: 12.18 × 24.11 mm.

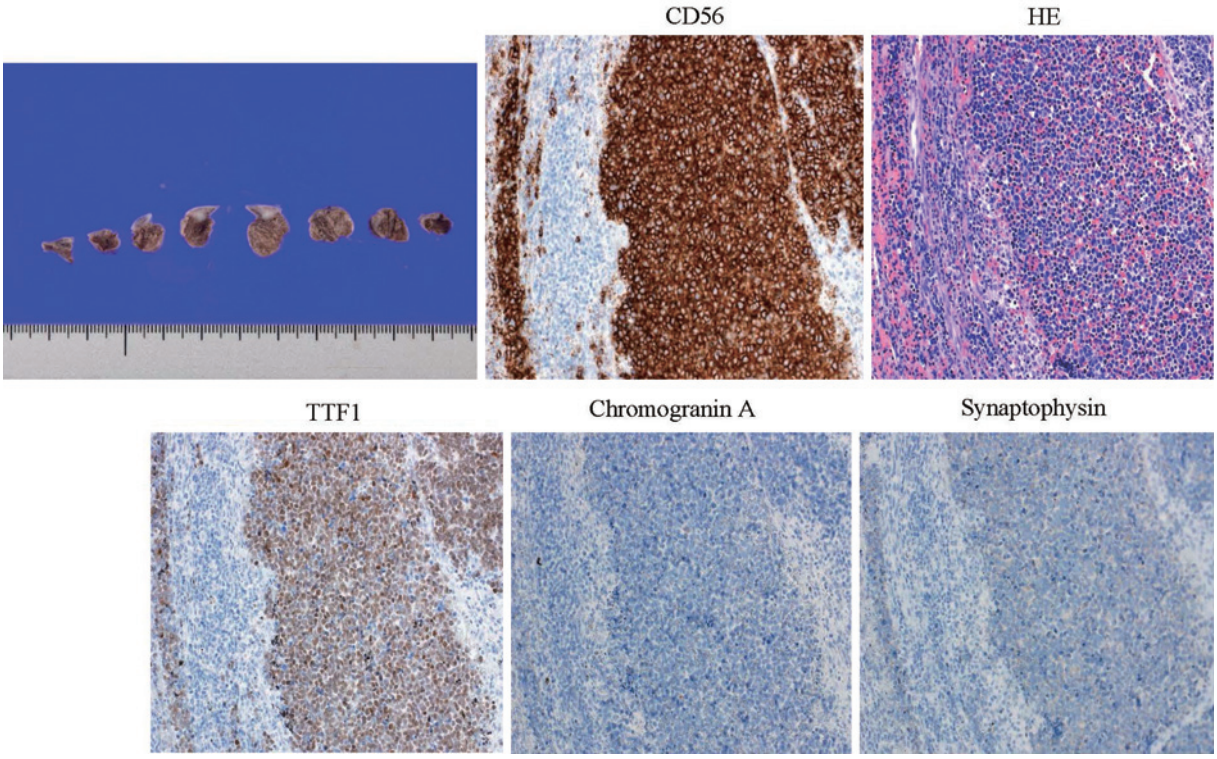

Figure 2

Tumor cells in the lymph nodes near the para-aortic arch were CD56-positive, TTF1-positive, chromogranin A-negative, and synaptophysin-weakly positive, which were consistent with small cell carcinoma.

Acknowledgments

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References

1) Darnell RB, Posner JB: Paraneoplastic syndromes involving the nervous system. N Engl J Med **349**: 1543-1554, 2003. doi: 10.1056/NEJMra023009.
2) Graus F, Delattre JY, Antoine JC, et al.: Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry **75**: 1135-1140, 2004. doi: 10.1136/jnnp.2003.034447.
3) Tamune H, Takeya H, Suzuki W, et al.: Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis. Am J Emerg Med **32**: 263-236, 2014. doi: 10.1016/j.ajem.2013.11.030.
4) Eeg-Olofsson O, Link H, Wigertz A: Concentrations of CSF proteins as a measure of blood brain barrier function and synthesis of IgG within the CNS in 'normal' subjects from the age of 6 months to 30 years. Acta Paediatr Scand **70**: 167-170, 1981. doi: 10.1111/j.1651-2227.1981.tb05536.x.
5) Graus F, Vogrig A, Muñiz-Castrillo S, et al.: Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. Neurol Neuroimmunol Neuroinflamm **8**: e1014, 2021. doi: 10.1212/NXI.0000000000001014.
6) Brun G, Graber M, Mohr S, et al.: Acute Bulbar Palsy and Ophtalmoplegia Associated With Anti-GT1a IgG Antibodies. Neurologist 2021 Dec 30. doi: 10.1097/NRL.0000000000000407.
7) Kim JK, Kim BJ, Shin HY, et al.: Korean Inflammatory Neuropathy Consortium. Acute bulbar palsy as a variant of Guillain-Barré syndrome. Neurology **86**: 742-747, 2016. doi: 10.1212/WNL.0000000000002256.
8) Zekeridou A, Majed M, Heliopoulos I, et al.: Paraneoplastic autoimmunity and small-cell lung cancer: Neurological and serological accompaniments. Thorac Cancer 2019 Apr;10:1001-1004. doi: 10.1111/1759-7714.13009.
9) Samejima S, Tateishi T, Arahata H, et al.: A case of anti-Hu antibody- and anti-GluR epsilon2 antibody-

positive paraneoplastic neurological syndrome presenting with limbic encephalitis and peripheral neuropathy. Rinsho Shinkeigaku **50**: 467-472, 2010. Japanese. doi: 10.5692/clinicalneurol.50.467.

10) Ueda S, Iwanaga K, Wakahara T, et al.: A case of mediastinal lymph node cancer of unknown primary origin discovered in paraneoplastic neurological syndrome and positive for anti-Hu antibodies. The journal of the Japanese association for chest surgery **27**: 100-105, 2013.
11) Tanaka K: Paraneoplastic neurological syndromes with reference to anti-neuronal autoantibodies. Rinsho Shinkeigaku **50**: 371-378, 2010. Japanese. doi: 10.5692/clinicalneurol.50.371.
12) Uchuya M, Graus F, Vega F, et al.: Intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with antineuronal autoantibodies. J Neurol Neurosurg Psychiatry **60**: 388-392, 1996. doi: 10.1136/jnnp.60.4.388.
13) Binks S, Uy C, Honnorat J, et al.: Paraneoplastic neurological syndromes: a practical approach to diagnosis and management. Pract Neurol **22**: 19-31, 2022. doi: 10.1136/practneurol-2021-003073.
14) Holmes FF, Fouts TL: Metastatic cancer of unknown primary site. Cancer **26**: 816-820, 1970. doi: 10.1002/1097-0142(197010)26:4<816::aid-cncr2820260413>3.0.co;2-r.
15) Stewart JF, Tattersall MH, Woods RL, et al.: Unknown primary adenocarcinoma: incidence of overinvestigation and natural history. Br Med J **1**: 1530-1533, 1979. doi: 10.1136/bmj.1.6177.1530.
16) Ueshima Y, Kurioka H, Takumi C, et al.: Two Cases of Cancer of Unknown Origin Affecting the Hilar and Mediastinal Lymph Nodes. JJLC **44**: 245-249, 2004.
17) Miyashi K, Okumura N, Kokado Y, et al.: Metastatic thoracic lymph node carcinoma of unknown origin. JJLC **47**: 245-250, 2007.