Anti-SOX1 Antibody-Positive Paraneoplastic Syndrome Presenting with Subacute Cerebellar Degeneration and Lambert-Eaton Myasthenic Syndrome: A Case Report

Yung-Chun Cheng, Anna Chang, Wei-Chih Hsu

Abstract

Purpose: Paraneoplastic neurological disorders associated with autoantibodies are rare diseases, causing abnormal manifestations in the central or peripheral nervous system separately or simultaneously. Early recognizing the occurrence of paraneoplastic syndrome can lead to prompt and effective management.

Case Report: We presented a patient of subacute cerebellar degeneration with cachectic and bed-ridden status, who was proven to have positive SOX1 antibody. A coexisting Lambert-Eaton myasthenic syndrome was also documented by electrophysiological study.

Conclusion: Intensive and regular follow up for an occult malignancy is crucial in patients with SOX1 antibody. Coadministration of therapies for underlying malignancy and LEMS improve the functional disability.

Keywords: Paraneoplastic syndrome, Subacute cerebellar degeneration, Lambert-Eaton Myasthenic syndrome, SOX1 antibody.

Acta Neurol Taiwan 2021;30:74-77

INTRODUCTION

Paraneoplastic neurological disorders (PND) associated with autoantibodies are rare diseases, causing abnormal manifestations in the central or peripheral nervous system [1,2] and co-occurrence is not unusual [3]. Among patients with cancer without selection criteria, less than 1% develop PND. About 3–5% of patients with small cell lung carcinoma (SCLC), 15–20% with thymomas, and 3–10% with B-cell or plasma-cell neoplasms develop PND[1]. Though the clinical symptoms are varied, these neurologic disorders usually develop prior to the identification of cancer. Therefore, early clinical recognition of paraneoplastic syndrome can lead to prompt and effective management. Here, we report an anti-SOX (Sry-like high mobility group box) 1-positive patient who presented with subacute unsteady gait with cachexia coexisting with Lambert-Eaton myasthenic syndrome (LEMS) that was documented by electrophysiological study. Coadministrations of therapies for underlying

From the Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.
Received October 22, 2020. Revised January 22, 2021.
Accepted January 25, 2021.
Correspondence to: Wei-Chih Hsu, Department of Neurology, Shin Kong WHS Memorial Hospital, Taipei, Taiwan.
Email: hamp.london@msa.hinet.net

malignancy and LEMS have improved the functional dependence.

CASE REPORT

A 60-year-old female patient came with progressive gait disturbance, involuntary tremor of head and left upper limb, orthostatic dizziness, and sphincter incontinence for 9 months. Additionally, she had a body weight loss of 10 kg with cachectic appearance and general weakness.

Her mental status was normal. Neurological examination was notable for cerebellar signs, including hypometric saccadic and slow eye movement, multidirectional nystagmus, dysmetria and dysdiadochokinesia in limbs, truncal titubation at sitting position, positive rebound phenomenon, and 2 to 3Hz tremor in head and left upper limb. Cranial nerves examinations revealed facial diparesis and nasal voice. Muscle strength was grade 3 (MRC scale) in four limbs with general areflexia.

Basic blood and biochemistry profiles were normal. Tumor markers, thyroid function tests, autoimmune tests including erythrocyte sedimentation rate, rheumatoid factor, C3, C4, ANA, Anti-dsDNA, Anti-ENA screen, ceruloplasmin, IgG, IgA, IgM, lactate, creatine kinase, human immunodeficiency virus screen were unremarkable. Cerebrospinal fluid (CSF) analysis showed no cells and normal protein and glucose levels. CSF 14-3-3 protein was negative. CSF cytology showed no atypical cells. Brain Magnetic resonance imaging showed cerebellar atrophy (Fig 1).

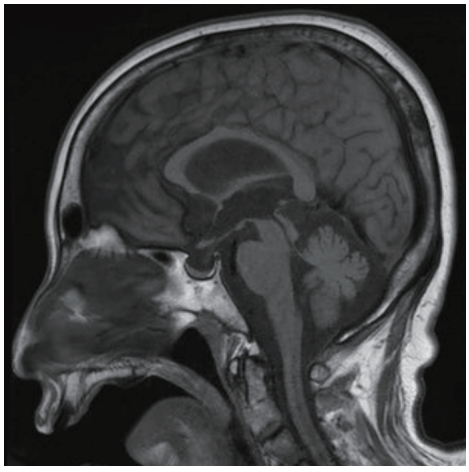

Fig. 1. Marked cerebellar atrophy in Brain MRI.

Qualitative serum test for paraneoplastic autoantibodies revealed positive anti-SOX1 antibody. The other onconeural antibodies, including anti-Amphiphysin, CV2, Ma2, Ri, Yo, Hu, Recoverin, Titin, Zic4, GAD65, and Tr were all negative. Nerve conduction studies showed low compound muscle action potential (CMAP) amplitudes with normal conduction velocities and F wave latencies in all motor nerves. The sensory conduction studies were all within normal limits.

The combination of anti-SOX1 autoantibody and unexpected diffuse low CMAP amplitudes with normal sensory nerve tests along with clinical manifestation of generalized limbs, bulbar, facial weakness led to the impression of LEMS. Repetitive nerve stimulation test (RST) showed a decremental response at 3 Hz and > 100% incremental response at 30 Hz in right abductor digiti minimi (Fig 2). The titer of anti-acetylcholine receptor antibody was normal. Whole body Computed Tomography (CT) scans of the chest, abdomen, and pelvis showed air-space consolidation with enhancement at left lower lobe of the lung and multiple lymph nodes in the mediastinum. Positron Emission Tomography–Computed Tomography (PET-CT) revealed two irregular nodules in the right upper lung and another one near the hilum region, which all of them had increased fluorodeoxyglucose (FDG) uptake. She underwent thoracoscopy biopsy and resection of left lower lobe, and the pathology showed only bronchiolitis and lymphoid hyperplasia in the mediastinal lymph nodes without malignant cells. Colonoscopy biopsy showed a 0.3cm sigmoid tubular adenoma.

She received 5 sessions of plasmapheresis on alternate days along with intravenous methylprednisolone pulse

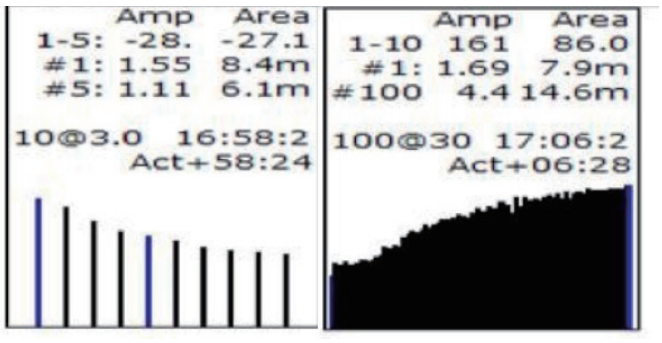

Fig. 2. Decremental response at 3 Hz and >100% incremental response at 30 Hz in repetitive nerve stimulation test.

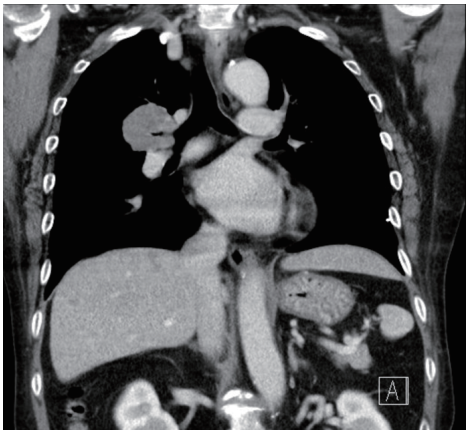

Fig. 3. A rapidly progressed lung mass (arrow) in chest CT 6 months later.

therapy 1000mg daily for 5 consecutive days, which were followed by oral prednisolone 1mg/kg daily and pyridostigmine bromide. Over the next four weeks, the respiratory function and muscle strength improved gradually. The muscle strength of both neck flexor and extensor were grade 5, proximal upper limbs were grade 4+, proximal lower limbs were grade 3 with less facial diparesis and nasal voice. Cerebellar signs remained unchangeable. She needed nasogastric tube for swallowing and chewing difficulty but did not require any noninvasive mechanical ventilation at discharge.

She had lost follow-up for 6 months after discharge, which led to the loss of timely chest CT scan. Chest CT was performed 6 months later and revealed rapidly progressed lung mass with multiple liver metastasis (Fig 3). Bronchoscopy biopsy confirmed the presence of SCLC. At the time of report, a total of three cycles of chemotherapy with carboplatin area-under-curve 5 on day 1 and etoposide 120 mg/m^2 on days 1, 2, 3 were administered. She currently presents an improvement in cerebellar function and could walk with assistance at home.

DISCUSSION

Anti-SOX1 antibody is an anti-glial nuclear antibody involving the Bergmann glia in the cerebellum and is found in almost half of the patients with paraneoplastic LEMS. The presence of anti-SOX1 antibodies in patients with LEMS predicts the presence of SCLC [4]. Clinically, these patients with LEMS have typical proximal weakness in the limbs, diplopia, and dry mouth. Electrophysiological tests, including nerve conduction tests and RST, are non-invasive and convenient tools for the diagnosis of LEMS. The characteristic electrodiagnostic features of LEMS include low amplitudes of CMAP, a decremental response at low frequency (3 Hz) and incremental response at high-rate stimulation (>10Hz) in RST.

Antibodies to voltage-gated calcium channel (VGCC) are detected in 85%–90% of patients with LEMS and nearly 100% of patients with LEMS and SCLC [5]. Not only LEMS, other paraneoplastic syndromes like cerebellar degeneration, encephalopathy and neuropathy are also associated with VGCC antibodies [6]. Like VGCC antibodies, the clinical manifestations of patients with anti-SOX1 antibody may be not limited to LEMS alone. Previous case reports indicated that the patients with anti-SOX1 antibody who presented with ataxia may have coexisting anti-Hu or CV2/CRMP5 antibodies. These antibodies are specific for paraneoplastic cerebellar degeneration [7]. Another patient with anti-Hu antibody had electrophysiological signs of LEMS, whose devastating cerebellar syndrome masked the symptoms of LEMS [8]. The immobility and cachexia of our patient also interfered with the clinical detection of LEMS, but she lacked the relevant autoantibodies of paraneoplastic cerebellar degeneration.

Because the symptoms of paraneoplastic syndrome often develop prior to the detection of malignancies, a thoracic CT or PET-CT should be used to detect SCLC in patients with LEMS. If the results are negative, a second screening should be done after 3-6 months [9]. Our patient had complete screening examinations initially and failed to find a definite malignancy, but the outbreak of SCLC with multiple metastases was noted six months later. This is consistent with the suggestion that an earlier screening program in 3 months is essential in high-risk patients.

The experience from our patient highlights four points. First, after the exclusion of treatable etiologies of subacute cerebellar syndrome, the consideration of a paraneoplastic source is imminent even if there are no significant clinical clues for occult malignancies. Second, RST is helpful for the diagnosis of LEMS in patients with anti-SOX1 antibody. Third, intensive and regular follow-up is crucial in patients with anti-SOX1 antibody. Finally,

coadministration of treating underlying malignancy and symptomatic management for LEMS may improve the functional conditions.

REFERENCES

1. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008; 7: 327–40.
2. Antoine J-C, Camdessanché J-P. Peripheral nervous system involvement in patients with cancer. Lancet Neurol 2007; 6: 75–86.
3. Darnell RB, Posner JB. Paraneoplastic Syndromes Involving the Nervous System. N Engl J Med 2003;349:1543-54.
4. Sabater L, Titulaer M, Saiz A, Verschuuren J, Güre AO, Graus F. SOX1 antibodies are markers of paraneoplastic Lambert–Eaton myasthenic syndrome. Neurology 2008;70:924–8.
5. Motomura M, Lang B, Johnston I, Palace J, Vincent A, Newsom-Davis J. Incidence of serum anti-P/O-type and anti-N-type calcium channel autoantibodies in the Lambert-Eaton myasthenic syndrome. J Neurol Sci 1997;147:35–42.
6. Balint B, Vincent A, Meinck H, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. Brain 1997; 120: 1279–1300. BRAIN 2018;141; 13–36.
7. Stich O, Klages E, Bischler P, Jarius S, Rasiah C, Voltz R, Rauer S. SOX1 antibodies in sera from patients with paraneoplastic neurological syndromes. Acta Neurol Scand 2012;125: 326–31.
8 Mason WP, Graus F, Lang B, Honnorat J, Delattre JY, Valldeoriola F, Antoine JC, Rosenblum MK, Rosenfeld MR, Newsom-Davis J, Posner JB, Dalmau J. Small-cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert–Eaton myasthenic syndrome. Brain 1997; 120: 1279–1300.
9. Titulaer MJ, Lang B, Verschuuren JJGM. Lambert–Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol 2011; 10: 1098–107.