SMALL-CELL LUNG CANCER PRESENTING WITH LAMBERT-EATON MYASTHENIC SYNDROME AND RESPIRATORY FAILURE

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Abstract: Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular disorder characterized by defective neurotransmitter release at presynaptic terminals. It is caused by an IgG autoantibody reacting against voltage-gated calcium channels. Severe LEMS complicated by ventilatory failure is rare. We report a case of small-cell lung cancer (SCLC) presenting with LEMS and ventilatory failure in a 67-year-old man who initially presented with progressive limb weakness for 6 months and tachypnea with shallow breathing for 1 week. LEMS was diagnosed through electrophysiologic studies. Chest radiography and computerized tomography showed a huge mass lesion over the left anterior and middle mediastinum with an encasement of the left pulmonary artery. Cytologic examination of ultrasound-guided fine needle aspiration disclosed SCLC. Successful treatment in combination with plasma exchange and chemotherapy resulted in dramatic tumor regression and LEMS remission, which were confirmed by chest radiography and electrophysiologic studies. This case suggests that plasma exchange and chemotherapy can be effective in treating SCLC with severe LEMS that produces ventilatory failure.

Case Report

This 67-year-old man had a 3-year history of prostate cancer treated with regular hormone therapy without evidence of tumor progression. He had a 2-year history of diabetes mellitus that was well controlled with oral hypoglycemic agents. He suffered from intermittent vertigo and vomiting 10 months before this admission. On this admission, chest radiography showed only slightly increased lung markings and fibrocalcified lesions over bilateral upper lung fields. Dysarthria and an unsteady gait had also developed. Vestibular and cerebellar dysfunction were diagnosed after brain imaging and neurophysiologic studies. Sensorimotor polyneuropathy was also diagnosed after nerve conduction velocity (NCV) study. The patient suffered from progressive ataxia and leg weakness, resulting in a bedridden status 6 months before admission.

The patient was brought to our department 1 week after the onset of tachypnea, with shallow breathing and progressive muscle weakness with quadriparesis, ptosis, dysarthria and dysphagia. Fever and productive cough with purulent sputum were also noted for 3 days. Physical examination revealed ptosis and localized wheezing in the inspiratory and expiratory phases over the left upper anterior chest. Neurologic examination showed grade 2–3 muscle power in the proximal muscles of the upper and lower limbs. Deep tendon reflexes were generally decreased.
Mildly elevated white blood cell count (9.24 x 10^9/L) with left shift (neutrophils, 80.9%), and marked elevations in serum lactate dehydrogenase (729 U/L) and C-reactive protein (3.21 mg/dL) were noted. There was no obvious serum electrolyte abnormality. Chest radiography showed a huge mass lesion over the left hilum with a widening mediastinum (Fig. 1). Computed tomography scanning of the chest revealed one mass lesion over the anterior and middle mediastinum with a left pulmonary trunk encasement.

Intravenous injection of amoxicillin (1,000 mg)/clavulanate potassium (200 mg) every 8 hours was given for suspected airway infection. However, ventilatory failure with CO₂ narcosis occurred the day after admission. Arterial blood gas analysis on an O₂ nasal cannula (3 L/min) showed the following: pH 7.27; PaCO₂, 68 mmHg; PaO₂, 134 mmHg; bicarbonates, 30.2 mmol/L; and BE, 2.4 mEq/L. Endotracheal intubation was carried out and the patient was transferred to the intensive care unit. Assist controlled mandatory ventilator support was given with the following values: fraction of inspired oxygen (FiO₂), 0.3; tidal volume, 500 mL; positive end-expiratory pressure, 5 cm H₂O; and respiratory rate, 10 per minute. Arterial blood gas analysis showed: pH 7.44; PaCO₂, 37 mmHg; PaO₂, 126 mmHg; bicarbonates, 25.2 mmol/L; and BE, 1.2. Cytologic examination of ultrasound-guided fine needle aspiration of the lung tumor disclosed SCLC. The compound muscle action potentials (CMAPs) of the right abductor digitii minimi muscle were extremely low (only 1 mV). During repetitive nerve stimulation at a frequency of 30 Hz, the CMAPs increased in size by about 230% of the initial response (Fig. 2). LEMS was diagnosed. Reactivity to anti-Hu antibody, one kind of anti-voltage-gated calcium-channel (VGCC) antibody, was negative, but other types of anti-VGCC antibodies were not tested.

The NCV study showed a superimposed sensorimotor polyneuropathy. Pressure on maximal inspiration (Pimax) was poor (-18 cm H₂O). SCLC with LEMS complicated with ventilatory failure was diagnosed. Other autoimmune profiles and serum electrophoresis were within normal limits. Fever and leukocytosis improved with antibacterial therapy. Plasma exchange with 150% of the patient's serum quantity (4 L) was carried out once on the 3rd day after the onset of respiratory failure. After plasma exchange, the patient received chemotherapy with cisplatin (80 mg/m²) on day 1 and etoposide (80 mg/m²) on days 1-3. Dramatic improvements in muscle power (from grade 2-3 to 4-5) and Pimax (from -18 to -50 cm H₂O) were noticed on the 4th day after respiratory failure. The patient regained muscle power and was extubated on the 8th day after the onset of respiratory failure. An intermittent, noninvasive, bilevel, positive airway pressure ventilator was used.

A second course of plasma exchange was carried out. The patient breathed independently at the beginning of the 4th week after the onset of respiratory failure. Follow-up chest radiography showed a marked decrease in tumor size (Fig. 3). NCV study showed improvement of the initial CMAPs (about 3 times the initial CMAPs of the previous NCV study). The incremental response during the repetitive stimulation test also became negative. The patient received a second course of chemotherapy with etoposide and cisplatin and was subsequently discharged. After discharge, muscle power was stationary and the patient was readmitted for scheduled chemotherapy. However, sudden onset of sputum impaction with cyanosis developed on the 3rd day after admission.

Intubation was carried out, but hypoxic encephalopathy was
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noticed. The patient was transferred to the chronic care center after tracheostomy and died 2 weeks later from sepsis.

Discussion

SCLC with LEMS presenting as respiratory failure is rare, although it is under-reported. In this patient, both prostate cancer and SCLC were diagnosed. Agarawal et al reported the association of LEMS in a patient with prostate cancer who recovered after bilateral orchidectomy and plasma exchange [5]. However, our patient had no evidence of tumor progression in prostate cancer with hormone therapy during the previous 3 years of follow-up.

The release of neurotransmitters at presynaptic motor nerve terminals depends on the influx of calcium through VGCCs [6]. IgG autoantibodies from patients with LEMS have been shown to block VGCCs and decrease the release of neurotransmitters. Such VGCCs are present at neuromuscular junctions, and in autonomic neurons and the central nervous system, particularly the cerebellum. Over 90% of patients with LEMS have antibodies against VGCCs [7]. In electrodiagnosis, CMAPs and post-activation exhaustion at frequencies between 1 and 5 Hz in repetitive nerve stimulation are seen in both LEMS and myasthenia gravis. In LEMS, however, CMAPs are often less than 10% of normal and increase to at least twice the size of their initial response during stimulation at frequencies between 20 and 50 Hz. All of these features were noted in this patient. VGCC autoantibodies may disappear in patients receiving immunosuppressive therapy, and levels usually fall if the underlying disease improves. However, VGCC autoantibody levels do not correlate well with disease severity [8]. SCLC cells are thought to be of neuroectodermal origin and contain high concentrations of VGCCs. Thus, an antibody with cross-reactivity and the ability to block VGCCs is produced, resulting in muscle weakness.

The cardinal characteristics of LEMS are muscle weakness, especially in the proximal muscles of the legs, and depressed tendon reflexes. Muscle strength increases temporarily after voluntary exercise. The onset of symptoms is usually gradual. Mild and transient cranial nerve symptoms are reported by 70% of patients. Ptosis, as in our patient, is the most common of the cranial nerve symptoms [6]. Autonomic symptoms, especially dry mouth, are experienced by 80% of patients [3]. These symptoms of LEMS may be provoked by systemic stress and infection. Subacute cerebellar degeneration was also reported to coexist with paraneoplastic syndrome with LEMS [9]. In this patient, LEMS presented initially as cerebellar dysfunction. Sensorimotor neuropathy, as in this patient, has also been reported as an SCLC-associated paraneoplastic syndrome [10].

The initial treatment should be aimed at any tumor present, because weakness frequently improves after effective cancer therapy [3, 4, 11]. When weakness is severe, plasma exchange may be used. Newsom-Davis et al described seven LEMS patients treated with plasma exchange [12]. There was no early improvement, but after approximately 2 weeks, muscle strength improved in most patients, then deteriorated again 1 month later. The effectiveness of treatment with plasma exchange followed by chemotherapy in severe LEMS with respiratory failure in SCLC remains to be established. Although treatment of the underlying malignancy is useful in long-term management, it does not provide immediate assistance for such patients. In this patient, plasma exchange and then chemotherapy with etoposide and cisplatin were initially given. Muscle weakness improved dramatically and breathing became independent before discharge.

In summary, this case of SCLC with an initial presentation of LEMS and paraneoplastic syndrome, resulting in muscle weakness and respiratory failure, suggests that plasma exchange and chemotherapy are effective treatments for this condition.

References


