Amyotrophic Lateral Sclerosis Associated with Sarcoidosis

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Abstract

We report a rare association of amyotrophic lateral sclerosis (ALS) with incidental pulmonary and muscle sarcoidosis. A 63-year-old woman presented with slowly progressive weakness and atrophy of the extremities starting from the left leg. The biopsy of a small mass in the left gastrocnemius revealed a typical sarcoid nodule. She was treated with corticosteroid for possible sarcoid neuromyopathy. In spite of the treatment, her clinical course was relentlessly progressive and she died of bulbar palsy. Autopsy revealed a loss of motor neurons in the anterior horn, vacuolar degeneration of the lateral funiculus, and noncaseating granulomas in paratracheal lymph nodes and lungs. No granulomatous lesion or cellular infiltration was found in the spinal cord.

Key words: sarcoid neuropathy and pseudopolyneuritic type of amyotrophic lateral sclerosis

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disease and even now its etiology is unknown. However, circumstantial evidence supports that autoimmune factors could play a part in the etiology of ALS (1). It has been reported that ALS is associated with autoimmune disorders such as hypothyroidism and paraproteinemia (2, 3). We present here a case of ALS, associated with sarcoidosis, which is a disorder mediated by an intense cellular immunity (4, 5). We also discuss the mechanisms including the possibility of immunological pathogenesis of ALS and sarcoidosis.

Case Report

A 63-year-old left-handed woman, who had a past history of congenital dislocation of the right hip joint, was admitted to the orthopedics department of our hospital in February 1997 because of weakness and numbness of the left leg with gait disturbance. The patient had been well until eleven months earlier, when uveitis and bilateral hilar lymph node enlargement on the chest X-ray were pointed out at a local hospital. A chest X-ray, obtained in our hospital on February 27, 1997, also showed some opacities around the bifurcation of the trachea with calcification (Fig. 1). One month before admission, she noticed muscle weakness of the left lower limb. She also noticed a mass lesion at the left calf. T1 and T2-weighted MRI of the left leg, obtained on March 18, 1997, showed a homogenous high signal mass in the gastrocnemius muscle (Fig. 2A, B). Biopsy of the intramuscular mass at the orthopedic service revealed noncaseating granulomas with Langhans' giant cells (Fig. 3A). The diagnosis of systemic sarcoidosis and sarcoidosis-related neuromyopathy was made and she was treated with oral administration of 40 mg prednisolone daily. In spite of the treatment, her neuromuscular symptoms did not respond. Muscle atrophy and weakness of the left leg progressed thereafter, with the further involvement of the contralateral leg. Then she was transferred to our service in July 1997.

A general physical examination on March 5, 1997 showed no remarkable findings. Neurologically, the patient was alert and well oriented to time, place, and persons with normal speech. The cranial nerves were intact from the IIInd to XIth nerve. Grip strength (right/left) was 24 kg/18 kg. Motor power (right/left) by MRC scale was graded as follows: biceps, 5/5; triceps, 5/5; wrist flexors and extensors, 5/5; iliopsoas muscle, 5/2; quadriceps, 5/5; hamstrings, 5/2; anterior tibial muscle, 5/ 2; gastrocnemius muscle, 5/3. Muscles of the left lower limb were mildly atrophic but no fasciculation was noted. Sensations were intact in all modalities. The deep tendon reflexes were slightly hyperactive in the upper extremities and hypoactive in the lower extremities with bilateral equivocal plantar responses.

The urine was normal, as were the results of routine hematologic, blood chemical, enzyme tests, and electrocardiographic findings. Serum calcium was 9.4 mg/dl. Serum creatine kinase was 64 U/l. Serum lysozyme was 9.3 µg/ml. Serum angiotensin-converting enzyme was 13.9 mg/dl. Serum γ-globulin was 1.14 g/dl. Serum microsomal antibodies and thyroglobulin antibodies were negative. Serum CD4+/CD8+ ratio was 3.18. Antiganglioside antibodies including anti-GM1 antibody were negative in serum and cerebrospinal fluid. All tests of cerebrospinal
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Figure 1. A chest X-ray film obtained in our hospital on February 27, 1997 showed opacities around the bifurcation of the trachea and hilar regions with mild calcification, and no reticular shadows in the lung fields.

fluid showed normal values. An MRI study of the spinal cord did not reveal any abnormalities. A nerve conduction velocity study showed no significant abnormalities except for that of the left peroneal nerve, which was decreased to 20.9 m/sec with the prolonged distal motor latency (8.88 msec) and the lower CMAP amplitude.

Intravenous pulse therapy of methylprednisolone, plasmapheresis, and oral administration of immunosuppressant did not change the course of her illness. She noted muscle atrophy of the right extremity and bilateral upper extremities, 2 to 3 months after admission. Four months after admission, she developed respiratory muscle weakness with bulbar palsy, and died of respiratory failure in April 1998. Autopsy was done 3 hours postmortem.

Macroscopically, swollen hilar lymph nodes, which measured from 0.5 to 2.0 cm in diameter, were found. Spinal anterior roots showed severe atrophic changes. Histological findings of the hilar lymph node and lung showed noncaseating granulomas with epithelioid cells and Langhans’ cells, which were consistent with pulmonary sarcoidosis (Fig. 3B). There was a marked loss of anterior horn cells, especially prominent at the level of the lumbar spinal cord (Fig. 3C). There were many axonal spheroids in the anterior horn (Fig. 3C). Bunina bodies were also noted in the residual neurons (Fig. 3C). Marked pallor of myelin staining and vacuolar degeneration was noted in the corticospinal tract of the lateral funiculus (Fig. 3D). No mononuclear cell infiltration or granulomatous lesion in the spinal cord or around the nerve roots was found.

Discussion

The present case showed progressive muscle weakness and atrophy of the extremities, starting from the left leg and extending to the right leg and then to the upper extremities, and finally she died of bulbar involvement. Although the deep tendon reflexes in the lower extremities were diminished, those in the upper extremities were hyperactive with bilateral equivocal plantar responses. The autopsy findings showed a marked loss of the spinal anterior horn cells with spheroid and intracytoplasmic inclusion bodies, so-called Bunina bodies. Vacuolar

Figure 2. A) MRI of the left gastrocnemius muscle obtained on March 18, 1997. The T1-weighted image (1.5 Tesla, TR/TE=500/12) showed a homogenous high signal lesion with a surrounding low intensity area. B) The MRI T2-weighted image (1.5 Tesla, TR/TE=4,500/96.0) also showed the homogenous high signal area surrounded by a low intensity area.
Figure 3. A) The gastrocnemius muscle biopsy showed noncaseating granuloma with epithelioid cells and Langhans' cell (HE stain, ×680). B) Autopsy specimen of the hilar lymph node showing Langhans’ cells, epithelioid cells, and lymphocytes (HE stain, ×680). C) Horizontal section of the lumbar cord showing a reduced population of anterior horn cells and proliferation of the glia (HE stain, ×1,360). The upper inset in 3C shows axonal spheroids in the anterior horn (HE stain, ×1,360). The lower inset in 3C shows intracytoplasmic inclusions, so-called Bunina bodies in the residual anterior horn cell (HE stain, ×680). D) The lateral funiculus of the lumbar cord displayed a loss of myelin and vacuolar degeneration (HE stain, ×680).

degeneration of the corticospinal tract in the lateral funiculus was noted. Therefore, we diagnosed a pseudopolyneuritic type of amyotrophic lateral sclerosis (ALS). Furthermore, this patient also suffered from pulmonary and muscle sarcoidosis. Noncaseating granulomatous lesions, which were negatively stained for tuberculous bacilli, were localized in the lungs, paratracheal lymph nodes and intramuscular tissue. Hilar and carina lymph nodes showed pigmentation and infiltration of lymphocytes with calcification, which were consistent with anthracosis.

In her early clinical stage, we had some suspicion of sarcoid neuropathy, as motor nerve conduction velocity studies revealed slowing in motor conduction velocity with reduction in amplitude of the left peroneal nerve. Although the involvement of the cranial nerves, especially the seventh nerve, is the most frequent manifestation of neurosarcoidosis, mononeuropathy of the extremities is a rare manifestation (6–8). And cauda equina syndrome, which is also rare and occasionally shows symptoms such as mononeuropathy (9, 10), was ruled out by the negative findings of MRI and CSF. Moreover, corticosteroid treatment did not bring any improvement of her symptoms, despite previously reported beneficial effects of steroid for neurosarcoidosis (6, 11). We could not find sarcoid nodules or cellular infiltrations in the spinal cord or nerve roots of the lumbosacral regions. We could not find any involvement of the spinothalamic tract throughout the cord. Therefore, the tentative diagnosis of sarcoid neuropathy to account for her early clinical symptoms was almost ruled out. It was suspected that axonal degeneration due to ALS and segmental demyelination secondary to compression neuropathy by the long bedridden state might contribute to reduction in amplitude, slowing in motor conduction velocity, and prolonged distal motor latency of the left peroneal nerve.

Although the etiology of ALS and sarcoidosis remains unknown, it has been suggested that cellular immunity might play a role in the pathogenesis of both disorders (2, 4, 11–13). Appel et al suggested that raised levels of immune-associated-positive T cells probably reflect activation of the immune system.
in ALS patients (11). Kawamata et al showed the infiltration of CD4+ and CD8+ cells into the degenerative pyramidal tract and anterior horn in the spinal cord of patients with ALS (12). Engelhardt et al also showed the infiltration of CD4+ and CD8+ cells into the perivascular and intraparenchymal regions (13). Furthermore, the CD4+/CD8+ ratio in blood from patients with sarcoidosis is likely low. However, in the present case, the level of the CD4+/CD8+ ratio was not low. No significant mononuclear cell infiltration in the spinal cord parenchyma or around the spinal nerve roots was noted. In our extensive literature search, we were unable to find any reported cases of ALS in association with pulmonary or systemic sarcoidosis. Thus, it was concluded that this was the first case report of ALS in association with incidental pulmonary and muscle sarcoidosis.

References