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Case Report

Amyotrophic lateral sclerosis associated with pleuroparenchymal fibroelastosis

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Abstract: An autopsy case of sporadic amyotrophic lateral sclerosis (ALS) associated with pleuroparenchymal fibroelastosis (PPFE), a rare form of idiopathic interstitial pneumonia, is reported. The patient, a 76-year-old man, presented with shortness of breath and dyspnea and died of progressive respiratory failure after a clinical course of 9 months. Muscle weakness and motor disturbance were mild, and the diagnosis of ALS was not established until one month prior to death. He had serum IgM-kappa monoclonal gammopathy (IgM: 1,232 mg/dL). Autopsy demonstrated ALS of the lower neuron-predominant type. The density of motor neurons in the spinal anterior horn showed a moderate decline, and many remaining neurons contained round inclusions that were immunoreactive for pTDP-43 (phosphorylated transactivation responsive DNA-binding protein of 43 kD) and ubiquitin. Betz cells and the pyramidal tracts were well preserved. The lung showed typical features of PPFE predominantly affecting the upper lobe: fibro-hyalinous thickening of the visceral pleura, a marked increase and aggregation of elastic fibers in the subpleural zone, and intra-alveolar collagenous fibrosis with an increase of elastic fibers in the alveolar septa. Although the complications from interstitial lung diseases including PPFE in ALS patients are usually regarded as incidental, PPFE is clinically important because of its markedly adverse influence on the clinical course. IgM-monoclonal gammopathy is another notable finding in the present case, which is occasionally seen in ALS patients, and the pathogenesis of PPFE is also considered to be associated with immunological derangements.

Keywords: Amyotrophic lateral sclerosis, pleuroparenchymal fibroelastosis, IgM-monoclonal gammopathy

Introduction

In most patients with amyotrophic lateral sclerosis (ALS), respiratory insufficiency is the immediate cause of death, and it is usually brought about by neurogenic atrophy of respiratory muscles. Coexistence of primary lung diseases, especially interstitial lung disease, inevitably has an adverse influence on the respiratory functions and clinical course of ALS patients. However, because the association of these primary lung diseases with ALS has usually been regarded as coincidental, previous literature relevant to this issue is very limited.

We report an autopsy case of sporadic ALS associated with pleuroparenchymal fibroelastosis (PPFE), a rare, recently described form of idiopathic interstitial pneumonia [1-3]. The association of ALS and PPFE has not previously been reported and may be a coincidence, but the complication of PPFE markedly aggravated the respiratory functions and led to an unexpectedly early death. This association is also interesting on considering the pathogenetic relationship between the two disorders, because there are some lines of evidence suggesting that immunologic abnormalities play a role in the pathogenesis of PPFE [4, 5], and, furthermore, the present patient had IgM monoclonal gammopathy of undetermined significance (IgM-MGUS).

Clinical history

The patient was a 76-years-old man, who consulted a physician complaining of shortness of breath, dyspnea, loss of appetite, and palpitation lasting for 8 months. His past history included rectal cancer, which had been extirpated 10 years previously. His respiratory distress slowly progressed, and swallowing difficulty also appeared. Respiratory function tests demonstrated ventilation impairment of the

restrictive type. Because the physician could not detect any apparent organic lesions of the lung to explain the symptoms, the patient was referred to our hospital.

On admission, he was 169 cm tall and weighed 48 kg. The respiratory sounds were weak, and movements of the thoracic cage were decreased. Computed tomography (CT) of the chest demonstrated apical pleural thickening, subpleural emphysematous changes in the upper lobes, and upward retraction of the pulmonary hilum. Mild bilateral pneumothorax was also noted. Respiratory function tests showed the following results: vital capacity, 0.91 L (25.1% of the predicted value); forced vital capacity, 0.86 L (24.3%); forced expiratory volume in one second, 0.84 L (29.9%); blood pH, 7.384; PaO_2, 78.3 mmHg; PCO_2, 57.4 mmHg; and HCO_3-, 33.5 mmol/L. Neurological examination demonstrated dysarthria, muscle weakness of the neck and upper extremities, muscle atrophy of all extremities, and fasciculations of the biceps brachii muscle, but all these neurological symptoms and signs were very mild. Pathologic reflexes were not elicited. Results of needle electromyography were consistent with a lower motor neuron lesion, and a diagnosis of definite ALS of the respiratory-onset type was made. Cognitive impairment was not apparent, and cranial CT or magnetic resonance imaging did not reveal any marked abnormalities of the brain.

A hematologic study demonstrated an increase of serum IgM to 1,232 mg/dL, IgM-kappa monoclonal gammopathy on immunoelectrophoresis, and an anti-nuclear antibody with a 1:80 titer. Values for IgG and IgA were within normal ranges. Bence-Jones protein of the kappa type was detected in the urine. Since bone marrow biopsy revealed no clonal proliferation of lymphocytes or plasma cells, the monoclonal gammopathy was considered to be consistent with IgM-MGUS.

The patient wished to be cared for at home and was discharged. However, his respiratory distress rapidly worsened thereafter, and he was readmitted with a diagnosis of aspiration pneumonia 4 days after discharge. Despite treatment with antibiotics, he died of respiratory failure 11 days later. The whole clinical course from the onset of respiratory symptoms to death was about 9 months.

Pathological findings

Neuropathologic findings were consistent with ALS of the lower neuron-predominant type. The brain (1,390 g) grossly appeared normal, and neither diffuse nor localized atrophy of the cerebral cortex was present. On microscopic examination, pyramidal neurons of the motor cortex, including Betz cells, were well preserved, and neither neuronophagia nor astrocytosis was found. The frontal and temporal cortices also did not show apparent neuronal loss, except for a small focus of degeneration in the transitional zone between the CA1 sector and subiculum of the anterior hippocampus. A small number of senile plaques, neurofibrillary tangles, and ghost tangles were found in the hippocampus. Immunohistochemical study using antibodies against pTDP-43 (phosphorylated transactivation responsive DNA-binding protein of 43 kD) (pS409/410, clone 11-9, Cosmo Bio, Tokyo, Japan, 1:3,000) and ubiquitin (clone 1B3, MBL, Nagoya, Japan, 1:200) demonstrated scattered neurons that contained intracytoplasmic inclusions in the CA1 sector and dentate granule cell layer of the hippocampus and in the parahippocampal cortex (ALS type 2a) [6]. Similar pTDP-43-positive inclusions were not observed in the frontal or temporal neocortex. The brain stem and cerebellum were unremarkable, except for a small focus of neuronophagia in the hypoglossal nucleus. No pTDP-43-positive inclusions were detected in the hypoglossal nucleus.

The spinal cord showed moderate loss of anterior horn cells at the thoracic and lumbo-sacral levels (the cervical cord was not available for examination) (**Figure 1A**). Remaining cells showed simple atrophy, and neurons showing chromatolytic changes or having Bunina bodies could not be detected. Many anterior horn cells contained intracytoplasmic round inclusions (**Figure 1Ba**) or coarse granules (**Figure 1Bb**), and a few cells contained skein-like inclusions. These inclusions or granules were immunoreactive for pTDP-43 and ubiquitin but not discernible on H&E-stained sections. Degeneration of the lateral or anterior cortico-spinal tracts was not observed. Skeletal muscles, including the diaphragm, showed mild neurogenic atrophy.

Major pathologic changes outside the central nervous system were confined to the lungs,

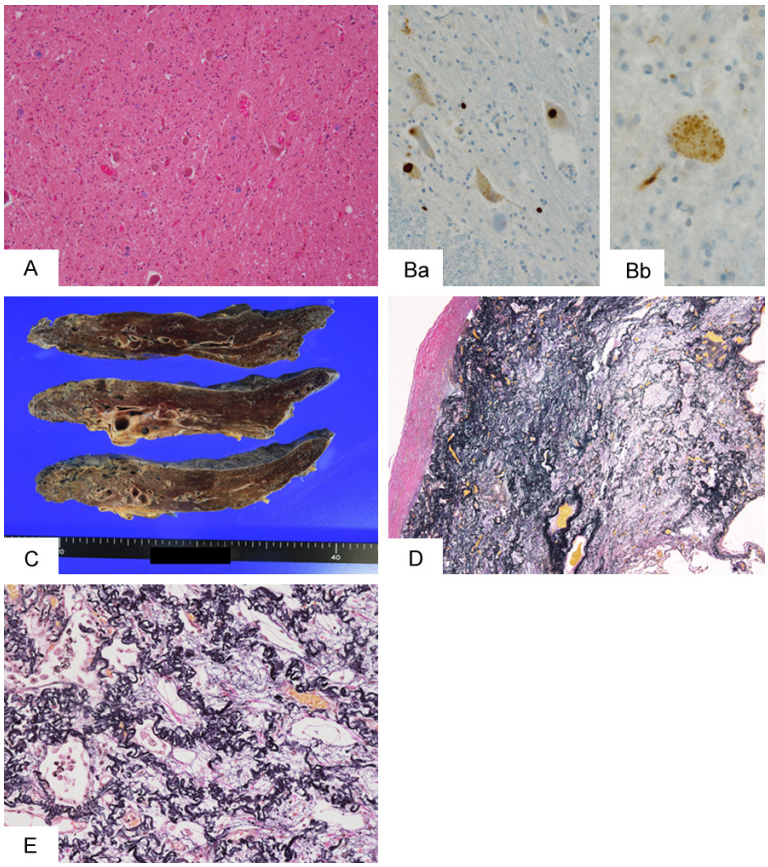

Figure 1. (A) Moderate neuronal loss with astrocytosis was noted in the spinal anterior horn (Hematoxylin-eosin stain, ×100). (B) Several remaining anterior horn cells contained pTDP-43-positive, intracytoplasmic round inclusions (a) or coarse granules (b) (Immunostain for pTDP-43; (a) ×200, (b) ×400). (C) Sagittal sections of the formalin-fixed left lung showed marked atrophy with collapse and fibrous thickening of the pleura of the upper lobe (left side of the figure). (D) The upper lobe showed fibro-hyalinous thickening of the pleura and a band-like, multilayered accumulation of elastic fibers in the subpleural zone (Elastica-van Gieson stain, ×40). (E) The subjacent area showed intra-alveolar, loose collagenous fibrosis with a marked increase of elastic fibers in the alveolar septa (Elastica-van Gieson stain, ×200).

which weighed 600 and 460 grams and showed typical features of PPFE. On gross examination, the upper lobes exhibited marked atrophy with collapse, which led to upward retraction of the pulmonary hilum, and fibrous thickening of the visceral pleura (**Figure 1C**). The middle and lower lobes showed a compensatory enlargement with congestion and edema. On microscopic examination, the pleura of the upper lobes showed fibro-hyalinous thickening, and the subpleural zone exhibited band-like sclerotic changes, which included alveolar collapse with a marked increase and multilayered accumulation of elastic fibers (**Figure 1D**). The subjacent area showed intra-alveolar loose collagenous fibrosis and a marked increase of elastic fibers in the alveolar septa (**Figure 1E**). These lesions showed abrupt transition to the slightly emphysematous lung parenchyma in the inner area. No abnormal lymphoplasmacytic proliferation or infiltration was noted in any organs including the brain or spinal cord.

Discussion

This patient's illness began with progressive respiratory distress of the restrictive type, and he died of respiratory failure 9 months after the onset of symptoms, only one month after the diagnosis of ALS had been established. A small percentage of ALS patients initially present with respiratory difficulty and show a relatively rapid course dominated by respiratory failure, without noticeable motor weakness or muscle atrophy of the extremities [7]. Motor neuron diseases including ALS should be considered in a differential diagnosis when patients present with respiratory distress of the restrictive type. The present patient was clinically considered to belong to this variant (respiratory-onset ALS) [7].

Neuropathologically, the present case was characterized by the absence of upper motor neuron involvement and appearance of many anterior horn cells containing pTDP-43-positive, round inclusions or coarse granules. In contrast, skein-like inclusions were relatively few. We recently reported another autopsy case of sporadic ALS, in which, while many skein-like inclusions were noted in anterior horn cells, round inclusions were absent [8]. Mori et al. proposed that the processes of forming skein-like and round inclusions were distinct and round inclusions tended to be seen more frequently in ALS cases with a short clinical course [9]. The presence of many remaining anterior horn cells that contain round inclusions or

coarse granules suggests that ALS was in an early stage of development in the present patient.

In addition to ALS, autopsy revealed the presence of PPFE. PPFE is a rare, slowly progressive disorder associated with a poor prognosis that clinically presents with restrictive respiratory disturbance and is pathologically characterized by fibrosis of the visceral pleura and band-like parenchymal fibroelastosis of the subpleural zone [1-3]. The lesions are accentuated in the upper lobe, so Amitani et al. [1], who first proposed it as a distinct entity, termed it "idiopathic pulmonary upper lobe fibrosis". Frankel et al. proposed the term of "PPFE" [2], and this disorder has been incorporated into the updated classification of idiopathic interstitial pneumonia as a rare subtype [10].

Previous reports concerning the association of primary lung disorders, especially interstitial lung diseases, with ALS are very limited and mostly restricted to a few recent reports of hypersensitivity pneumonitis [11] or interstitial pneumonia [12] caused by riluzole therapy. This is chiefly because the association of ALS with interstitial lung diseases has been considered merely fortuitous. In the late clinical stages of ALS, respiratory failure almost inevitably takes place, which is mainly caused by the restriction of dilatation of the thoracic cage due to atrophy of respiratory muscles including the diaphragm. In the present case, while neurogenic muscular atrophy remained mild, extensive subpleural fibroelastosis by PPFE markedly aggravated the ventilation impairment. The ranges of symptoms and progression of disease can vary among patients with PPFE [1, 3]. As seen in the present case, some patients show rapid aggravation of symptoms after a long, relatively indolent clinical course.

The etiopathogenesis of PPFE remains unknown, but it can secondarily occur in recipients of organ transplantation or hematopoietic stem cell transplantation [4]. The histopathologic features of PPFE have also recently been noted as manifestations of autoimmune disease-related pulmonary interstitial disorders [5]. These reports suggest that various immunological disorders including autoimmunity are associated with the pathogenesis of PPFE. Regarding this, an interesting feature of the present case was the presence of IgM-MGUS. IgM-MGUS is characterized by a low level of IgM monoclonal gammopathy and absence of lymphoproliferative disorder [13]. Monoclonal gammopathy, particularly the IgM type, is known to more frequently occur in patients with ALS than in the general population [14]. Several autopsied cases of the association of these two disorders have been reported, but the causal relationship between the two remains obscure [15, 16]. Suzuki et al. suggested the possibility that pTDP-43 accumulated secondarily to immunological derangement or through paraneoplastic mechanisms [16]. In our case, the patient had an anti-nuclear antibody in the serum. Monoclonal gammopathy is occasionally seen in patients with autoimmune disorders and is known to exhibit auto-antibody reactivity [15, 17, 18]. Immunological derangements inducing an autoimmune phenomenon might play a role in the pathogenesis of ALS in a subgroup of patients [16]. Considering that the autoimmune phenomenon might be related to the pathogenesis of PPFE [3, 5], it is possible that IgM-MGUS is implicated in the pathogenesis of PPFE. The coexistence of ALS, PPFE, IgM-MGUS, and antinuclear antibody in the present case therefore may not be coincidental.

Disclosure of conflict of interest

None.

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