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Monoclonal gammopathy with both nemaline myopathy and amyloid myopathy

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Abstract

Monoclonal gammopathies due to plasma cell dyscrasias can induce diverse rare neuromuscular disorders. Deposition of monoclonal antibody light chains in skeletal muscle causes amyloid myopathy. Monoclonal gammopathy is occasionally associated with sporadic late-onset nemaline myopathy. Here we report a monoclonal gammopathy patient with both sporadic late-onset nemaline myopathy and amyloid myopathy. The diagnoses were based on immunofixation electrophoresis of urine, and serum for free light chain assay, Congo red staining and Thioflavin S staining of muscle biopsies, as well as immunohistochemical staining and electron-microscopic observation. Nemaline myopathy and amyloid myopathy can present in the same patient with monoclonal gammopathy.

Keywords: Monoclonal gammopathy; Nemaline myopathy; Amyloid myopathy; Immunofixation electrophoresis; Free light chain assay; Thioflavin S staining

1. Introduction

Plasma cell dyscrasias are a heterogeneous group of hematological disorders characterized by abnormal proliferation of monoclonal plasma cells. Monoclonal gammopathies are conditions in which excessive amounts of immunoglobulins are produced by a cell clone stemming from a single pro-B germ cell. The conditions can be malignant, pre-malignant, or benign. Malignant monoclonal gammopathies include multiple myeloma, plasmacytoma, malignant lymphoproliferative disease, heavy-chain disease, primary amyloidosis, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome. The pre-malignant forms of monoclonal gammopathies are characterized by the presence of a clonal mass that has not reached a level that can be defined as a malignant state. Monoclonal gammopathy of undetermined significance is an example of a benign process with malignant potential [1].

Neurological manifestations of an underlying plasma cell disorder can range from very mild symptoms to life-threatening complications. Clinical implications are typically greater with central nervous system involvement, but the peripheral nervous system is more commonly affected [2]. While muscle diseases associated with monoclonal gammopathies are rare, amyloid deposition of monoclonal antibody light chains in skeletal muscles is gradually recognized [3,4]. Amyloid distribution within the muscles can span the perimysial, perivascular, or endomysial areas. Amyloid myopathy (AM) is classically characterized by mild proximal weakness, macroglossia, and muscle pseudohypertrophy or palpable muscle masses. A non-classical phenotype of amyloid myopathy has also been described that presents with more severe progressive weakness without macroglossia or pseudohypertrophy [5,6]. Sporadic late-onset nemaline myopathy (SLONM) is an infrequently recognized myopathy initially described in 1966 [7]. Clinical features of SLONM include sub-acutely evolving weakness occurring in adulthood, with clusters of nemaline rods in muscle fibers. SLONM is frequently associated with monoclonal gammopathies [8–11] and human immunodeficiency virus (HIV) infection [12]. Traditionally, HIV-associated SLONM responds to immunotherapy, but the combination of SLONM and a monoclonal gammopathy is predictive of an unfavorable outcome [11]. However, to our best knowledge, monoclonal gammopathy with both nemaline myopathy and amyloid myopathy in the same patient has not been reported to date. Here, we report a patient with monoclonal gammopathy with amyloid deposition and clusters of nemaline rods in skeletal muscles, who responded well to intravenous immunoglobulin (IVIG) and prednisone.

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2. Methods

We obtained detailed clinical information on the patient's age of onset, progression of disability, and clinical manifestations. The patient's workup included routine blood tests, magnetic resonance imaging (MRI), electromyography (EMG), cerebrospinal fluid analysis, bone marrow biopsy, and muscle biopsy.

A biopsied specimen of the left biceps muscle was flash-frozen in liquid nitrogen-cooled isopentane, an additional specimen was embedded in paraffin, and another specimen was placed in glutaraldehyde for electron microscopy. To detect amyloid deposits in the muscle specimen, we used Congo red staining in combination with polarized and fluorescent light, as well as thioflavin S (THS) staining [13], of paraffin sections. Immunostaining of paraffin sections was performed to specifically detect kappa and lambda chains.

The use of clinical information and human-derived material in this study was approved by the Ethical Committee of Xuan Wu Hospital, Capital Medical University, Beijing, China.

3. Results

3.1. Clinical features

A 66-year-old man with no family history of myopathy presented with a 10-month history of progressive proximal limb weakness and atrophy. The patient first noticed leg muscle weakness and had difficulty in climbing stairs. The weakness gradually worsened. Two months later, he needed assistance in rising from a chair and had difficulty in raising his arms and combing his hair. He had bilateral atrophy of the thighs and proximal arm muscles and atrophy of scapular and pelvic girdle muscles. He was able to chew, swallow, and breathe normally and had no muscle pain, skin rash, arthritis, fatigue intolerance, or cardiopulmonary symptoms. The only symptom associated with muscle weakness was a 2.5-kg weight loss. He had been diagnosed with hypertension 10 years ago and showed signs of brain ischemia 2 years ago. The strength of both proximal upper and lower limbs on the Medical Research Council (MRC) scale was 3/5, whereas distal limb muscles as well as facial, extraocular, and neck muscles were uninvolved. However, there was areflexia in all four limbs. Sensory examination was normal.

3.2. Routine blood tests

Results of serological tests for anti-HIV, anti-hepatitis C virus, anti-acetylcholine receptor, and anti-nuclear antibodies were negative. Serum creatine kinase (CK) levels were elevated to 1100–1400 U/L (normal range 18–198 U/L).

3.3. Immunofixation electrophoresis and serum free light chain assay

Serum protein immunofixation electrophoresis was performed twice, but it failed to detect a monoclonal abnormality. Urine immunofixation electrophoresis found free monoclonal kappa paraprotein. The kappa light chain protein concentration in 24 h total urine was 19.5 mg/dl, compared to a normal range of 0.0–1.85 mg/dl. A serum free light-chain (FLC) assay revealed a 26-fold elevation of the free kappa chain protein concentration, which reached 505 mg/L (normal range 13.30–19.40 mg/L). The concentration of lambda chain protein in blood was normal, resulting in a kappa/lambda ratio of 80:1.

3.4. Muscle biopsy

A biceps muscle biopsy specimen stained with the modified Gömöri trichrome staining showed numerous fine reddish granules in the sarcoplasm of some fibers (Fig. 1A), and electron microscopy (EM) showed these granules to be nemaline rods (Fig. 1B). We also found scattered ring-like structures surrounding individual myofibrils (Fig. 1C), which stained positively with oxidative and glycolytic stains but did not react with ATPase. Some ring-like structures were also present in saw-tooth fibers (Fig. 1D). Congo red staining did not show amyloid deposition when viewed under polarized light. Congophilic amyloid deposits were visible in the perimysium under fluorescent light (Fig. 1E). These were not detected in the abnormal ring-like structures and blood vessels. However, both ring-like structures, including the saw-tooth shaped circumference of amyloid deposits and blood vessels, were stained by thioflavin S staining (Fig. 1F). Necrotic or regenerating fibers were present without inflammation. Further immunohistochemical investigation for kappa and lambda antigens showed the sarcolemma of most muscle fibers to be immunoreactive for the kappa light chain, but not for the lambda light chain (Fig. 1G). Kappa light chain deposition was seen in the abnormal rings encircling scattered myofibrils and saw-tooth myofibrils, which corresponded to the amyloid deposits revealed by thioflavin S staining. Amyloid deposition in the saw-tooth myofibrils was confirmed by EM (Fig. 1H). Lambda staining was negative (data not shown).

3.5. Bone marrow biopsy

No lytic bone lesions or mass lesions were found on computer tomographic or positron emission tomographic scans of the chest, abdomen, and pelvis. Bone marrow biopsy revealed a monoclonal kappa-restricted plasma cell population, which accounted for 7.5% of the total marrow cells.

3.6. Other studies

Needle electromyography of the right deltoid, and the right and left vastus medialis muscles revealed a myopathic pattern with fibrillation potentials and positive sharp waves, low amplitude, and short duration of motor unit action potentials. Needle electromyography of the right pollicis brevis and tibialis anterior showed fibrillation potentials. Sensory and motor nerve conduction in the upper and lower extremities was normal. Muscle MRI revealed diffuse involvement of the thigh muscles except for the sartorius, gracilis, and rectus femoris. Results of electrocardiography, echocardiography, and pulmonary function tests were normal.

3.7. Treatment

The patient received monthly IVIG at 30 g (0.4 g/kg body weight) each time for 5 sequential days, for a total of 3 months. Because his muscle weakness had rapidly progressed, he was