Rippling Muscle Syndrome Preceding Malignant Lymphoma
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Abstract
A 46-year-old woman presented with rippling muscle phenomenon. She complained of uncomfortable muscular stiffness of extremities and abdominal wall. Muscle contraction was easily elicited by percussion, which was visible from the surface and propagated in a rolling manner. The mounding (or myoedema) phenomenon was also remarkable. Three years later, malignant lymphoma (histologically, lymphoplasmacytoid lymphoma) was found in the sacrum. The lymphoma subsided with treatment by vincristine, cyclophosphamide, doxorubicin and prednisolone. Serum IgG as well as creatine kinase values were normalized. The rippling phenomenon also responded to the treatment. The present rippling muscle syndrome might be of a paraneoplastic or autoimmune origin related to lymphoma, although the evidence seemed indirect. We discussed the role of the internal membrane system of the skeletal muscle in the pathogenesis of rippling muscle.

Case Report
A 46-year-old woman (born January, 1947) had noticed a gradual increase of her bilateral calf from several years before and complained of muscular stiffness of extremities and abdominal wall. A family physician found that her serum creatine kinase (CK) value was 1,004 IU/l (normal range is less than 150) and she visited our clinic for evaluation. She was 160 cm tall and 49 kg by weight. She was alert and cooperative and was normal by the general physical examination. Function of cranial nerves was normal as well as gait and posture. The deep tendon reflex seemed more brisk than normal. Pathological reflexes were absent. Sensory function was normal. Bilateral calf muscles were hypertrophic, but no fatiguability, muscular weakness or atrophy was noticed. By palpation, her muscle was felt firm. A marked mounding was elicited by tapping with a reflex hammer on the biceps brachii and gastrocnemius muscle. When the surface of the calf or thigh was tapped with a hammer, the muscle mass readily contracted and a wave of contraction propagated to the distant part. Later, it was confirmed that this contraction wave was electrically silent. Her past history was not contributory. In her family history, her father suffered from cancer of the biliary tract. Her elder sister suffered from breast cancer. There was no neuromuscular disease in any family members.

Laboratory studies
Serum CK was 2,287 IU/l and lactate dehydrogenase was 41 IU/l (normal; 103–190). Serum cholesterol was 297 mg/dl and HDL cholesterol was 108 mg/dl. Serum protein, creatinine, urea nitrogen, uric acid, bilirubin, electrolytes, liver enzymes, thyroid hormones, and anti-nuclear antigen were all within normal range. Blood count and urinalysis were also normal. Autoantibodies, such as anti-Ach receptor, anti-ryanodine receptor or Jo-1 were not examined.

Electrophysiology
On EMG using a concentric needle, fibrillation potentials appeared at rest in the biceps brachii and quadriceps femoris muscle. At insertion, no myotonic discharge was recorded, although insertion activity of less than 0.2 mV in amplitude and 0.3 seconds in duration was recorded in the flexor carpi ulnaris muscle. During a volitional activity, low amplitude, short du-
ration or polyphasic motor unit potentials (MUP) were recorded, which were intermingled with normal MUP. Amount of MUP was normal. The motor and sensory nerve conduction study were normal. These studies suggested a myopathic process without myotonic discharges. In recording with needle or surface electrodes, the propagated muscle contraction was void of action potential, demonstrating that the muscle activity was electrically silent.

**Muscle pathology**

Histological examination of the biopsied biceps brachii muscle showed a mild variation of muscle fiber diameter. A few small angular fibers were observed, which were condensed stained by the non-specific esterase method. There were a few necrotic or regenerated fibers as well as fibers with central nuclei. Distribution of abnormal muscle fibers was uneven among different muscle fascicles. There was no abnormality in the fiber type distribution. Muscle pathology consisted of both minor neuropathic and myopathic changes. A conventional electronmicroscopic study disclosed abundant vacuoles between myofibrils, which might originate from sarcoplasmic reticulum or t-tubules (Fig. 1). The t-tubule itself was dilated and prominent. Glycogen granules seemed slightly increased. Structure of myofibrils was normal.

**Skinned muscle fiber study**

Using the skinned muscle fiber preparation, activity of calcium ion (Ca²⁺) uptake by the sarcoplasmic reticulum (SR) and contracture by caffeine were analyzed (7). The Ca²⁺-accumulating capacity by the SR was normal and the response to caffeine was also normal, suggesting that the Ca²⁺-induced Ca²⁺-release (CICR) mechanism of the SR was intact.

**Clinical course**

Muscular stiffness and discomfort responded to oral dantrolene sodium to some extent. At 49 years by age, low back pain appeared and gradually became aggravated in next 5 months. MRI examination disclosed a mass lesion (75×90×40 mm) in and around the sacrum. The patient was admitted on May 22, 1997 first to an orthopedic ward and then to a hematological ward. Pathological studies of the biopsied mass showed a homogeneous proliferation of middle-sized atypical lympho-

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**Figure 1.** Electronmicrograph of the biceps brachii muscle (30,000×). A) Many vacuoles were observed between myofibrils (arrows). B) Some t-tubules was dilated and prominent (asterisks). Glycogen granules seemed slightly increased.
cytes intermingled with occasional plasma cells. There was no follicle formation, nor structure of the lymph node. Histological diagnosis was lymphoplasmacytoid lymphoma according to the updated classification of Kiel (8). Serum IgG was increased to 4,025 mg/dl and M-component of IgG λ type was detected. Hematologists, who cared for the patient, preferred diagnosis of multiple myeloma (IgG λ type), since Bence-Jones λ protein was detected in urine. Tumor cells had already infiltrated to the bone marrow, pelvic space, ribs, skull and several thoracic and lumbar spines. A combination of vincristine sulfate, cyclophosphamide, doxorubicin-HCl and prednisolone was administered in six courses. During the period of chemotherapy, the size of the sacral mass became much smaller, and the serum level of IgG was reduced from 4,025 mg/dl to 1,156 and CK also decreased from 456 IU/l to 133. The rippling phenomenon almost disappeared and mounding was less marked. Anti-oncotic therapy of malignant lymphoma was continued on an outpatient basis.

Discussion

Rippling muscle

The main clinical features of the inherited rippling muscle disease were muscle stiffness/myalgia, percussion-induced muscle mounding, muscle rippling and serum CK elevation. The rippling itself however, is not a prerequisite and the combination of symptoms may vary among the same family member (2, 9, 10). In the present case, the calf muscle was hypertrophic and the consistency of the muscle was generally increased. The mounding phenomenon was marked and the deep tendon reflex seemed much brisk without pathological reflexes. A mechanical stimulus elicited muscle contracture easily and the contracture spread in a rolling manner (rippling). Here, contracture means muscle contraction without the accompanying electrical activity. Serum CK values were moderately and consistently increased. These observations clearly showed that the patient had features of the rippling muscle disease. In the present case, the rippling muscle was electrically silent as in cases reported by Muller-Felber et al (5). This was contrast to the report of Vernino et al, where the rippling phenomenon was associated with electrical discharges in one of 3 cases presenting myasthenia gravis and muscular hyperexcitability (6). We considered chronic polymyositis, neuromyotonia (Issacs syndrome) and cramp-fasciculation syndrome as candidates for the differential diagnosis. The fibrillation potential and myopathic EMG might be consistent with polymyositis. But no clinical muscular weakness or atrophy was detected. The muscle pathology showed minimal neuropathic and myopathic changes without any cellular infiltration or inflammation. Therefore, chronic polymyositis was considered unlikely. An increased insertional activity other than fibrillation potentials has been observed in another case of rippling muscle disease (Masahiro Sonoo, Department of Neurology, Teikyo University Medical School: personal communications, September 19, 2001). But its significance remains unclear. In the muscle pathology, the distribution of abnormal muscle fibers such as angular or necrotic ones was uneven among different fascicles and this might suggest a simultaneous neurogenic influence, however, the implication was also unclear. In an electron microscopy of the inherited rippling muscle disease, infoldings of the sarclemma, honeycomb structures or multiple vacuoles related to T-tubule were described (2, 11, 12). Intermyofibrillar vacuoles and prominent T-tubules were observed in this case.

Pathogenesis

Rippling muscle disease (RMD) is either familial or sporadic. In some families, the responsible gene was localized to 1q41-42 (RMD1) (13). But RMD in other families is not linked to the chromosome 1 locus (9, 10). In a recent paper, RMD was caused by missense mutations of caveolin 3 gene (14). The rippling muscle phenomenon was complicated with myasthenia gravis and thymoma in other reports (4-6). In these instances, the rippling phenomena responded to immunosuppressive therapies, suggesting its autoimmune origin. So, we prefer the term "rippling muscle syndrome" to differentiate it from the inherited disease. Although the present case was sporadic, it was not definite yet whether the rippling phenomenon was genetic or acquired. The rippling phenomenon preceded 3 years before malignant lymphoma was discovered. The patient had noticed enlargement of her calf even earlier. However, chemotherapy reduced muscle symptoms, serum CK and serum IgG level. These observations might suggest the rippling muscle of present case was a paraneoplastic or autoimmune nature, although the evidence was indirect and autoantibody was not delineated. Moreover, it might be also possible that oncostatic agents attenuate E-C coupling itself. Pathological diagnosis of the biopsied tumor was lymphoplasmacytoid lymphoma (Kiel), but other clinical features were those of "multiple myeloma". So far, there seems to be no report of rippling muscle syndrome in malignant lymphoma or multiple myeloma.

Site of abnormality

Autoantibodies to high molecular weight muscle protein were reported in the rippling muscle syndrome (15). Epitopes of these autoantibodies are still unclear. It seemed possible that the internal membrane system of skeletal muscle could play a primary role for following reasons. The dilated T-tubules, which were shown by electron microscopy, may support this hypothesis. Natori demonstrated a spreading muscle contraction on the Natori’s skinned muscle fiber placed in oil (16). This spreading contraction could be an in vitro model of the rippling phenomenon. It seems important that the spreading contraction had occurred in the skinned fiber preparation, where the surface membrane had already been removed, but the T-tubule and SR remained. We also showed that the mounding was induced in vitro on the depolarized and/or T-SR junction-uncoupled muscle if the SR remained intact, i.e., Ca²⁺ was stored in the SR (17). According to Ricker et al, spreading speed of the rippling was 0.6 m/sec, a velocity that is 10 times slower than muscle fiber conduction velocity (2). It seems clear that a mechanical stimulus elicits local contraction, which also triggers contracture in the neighboring muscle fibers. A mecha-
sensitive receptor might exist in the t-tubule or SR, which induces \( \text{Ca}^{2+} \)-release from the SR when activated. CICR mechanism of the SR worked normally in the present case, but there are likely other unknown modes of regulation of the \( \text{Ca}^{2+} \)-release. The mechanism of pathological exaggeration and propagation of the contracture needs further study.

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**References**


