

Paraneoplastic Anti-3-hydroxy-3-methylglutary-coenzyme A Reductase Antibody-positive Immune-mediated Necrotizing Myopathy in a Patient with Uterine Cancer

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Abstract

We report the case of a 69-year-old woman with proximal limb muscle weakness, who received postoperative chemotherapy for uterine cancer. Her serum creatinine kinase level was high (10,779 mg/dL) and a muscle biopsy from her left biceps revealed various sizes of muscle fibers accompanied by necrotic and regenerating fibers. She was positive for anti-3 hydroxy-3-methylglutary-coenzyme A reductase (anti-HMGCR) antibodies, but negative for anti-signal recognition particle (anti-SRP) antibodies. She was diagnosed with immune-mediated necrotizing myopathy (IMNM) and treated with prednisolone.

Our findings indicate that not only drug-induced myopathy but also paraneoplastic myopathy can be involved in the pathogenesis of IMNM.

Key words: immune-mediated necrotizing myopathy, HMGCR, paraneoplastic syndrome, uterine cancer, steroid therapy

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Introduction

Immune-mediated necrotizing myopathy (IMNM) (1) is a novel clinical type of inflammatory myopathy that is characterized by the presence of anti-signal recognition particle (anti-SRP) and anti-3 hydroxy-3-methylglutary-coenzyme A reductase (anti-HMGCR) antibodies (2). Anti-HMGCR antibodies are induced by statins, which are HMGCR inhibitors (2). However, approximately 30% of anti-HMGCR antibody-positive IMNM patients have not been exposed to statins (2-5); other risk factors may include malignancies and collagen diseases (6-8). We herein report a case of anti-HMGCR antibody-positive IMNM that occurred in association with uterine cancer.

Case Report

A 69-year-old Japanese woman was admitted to our hos-

pital with proximal limb muscle weakness. She had been diagnosed with uterine cancer (cervical squamous cell carcinoma, stage IIIA) four years previously and had received postoperative chemotherapy [tegafur-uracil (600 mg/day)]. This postoperative chemotherapy was continued until the onset of muscle weakness. After the onset of proximal limb muscle weakness, her serum creatinine kinase (CK) level increased to 10,779 mg/dL-this was possibly due to chemotherapy. However, her symptoms remained after the cessation of chemotherapy. At 4 months after the onset of symptoms, she was admitted to our hospital for further evaluation.

At admission, her blood pressure (114/70 mmHg), heart rate (75 beats per minute) and body temperature (36.5°C) were within the normal ranges. Her bulbar conjunctivae were pale. Otherwise, there were no abnormal physical findings (thyroidal swelling or tenderness, specific rash, or peripheral limb edema). Neurological examinations showed proximal limb motor weakness (manual muscle test 3-4/5)

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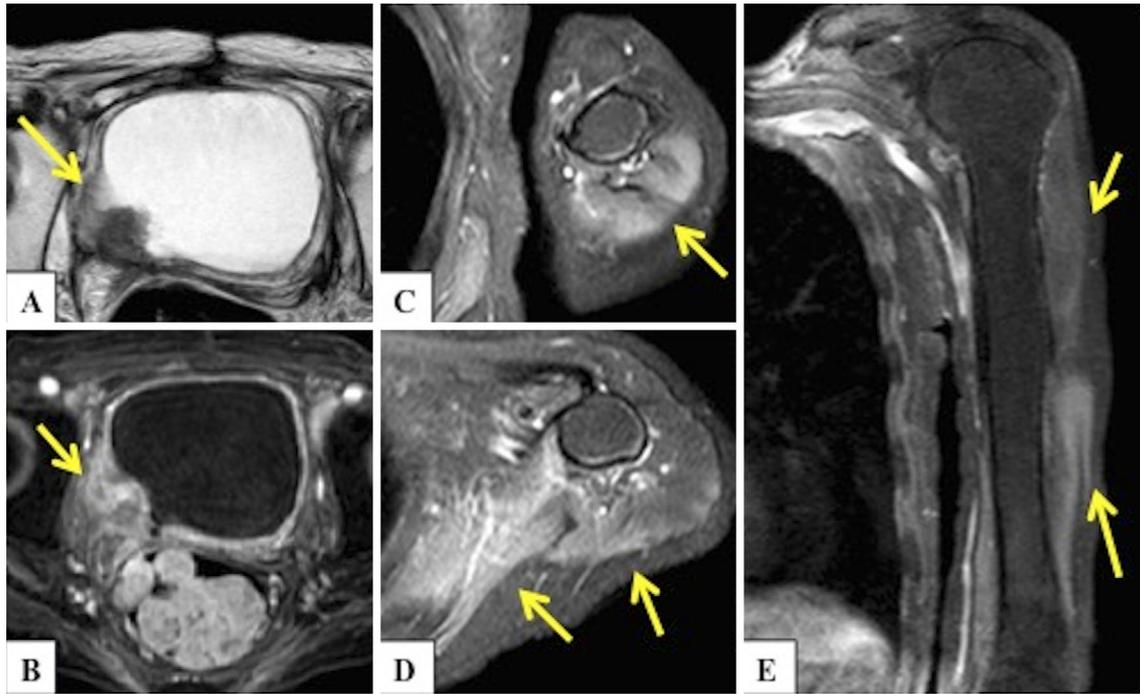


Figure 1. A: T2-weighted MRI showed an abnormal low-signal mass lesion toward the back from the head side of the bladder. B: This lesion showed an internal heterogeneous contrast effect on T1 with gadolinium enhancement. C, D, E: Short tau inverted recovery imaging on muscle MRI revealed high signal lesions on the left side of the triceps (C; axial view, E; coronal view) and latissimus dorsi (E; axial view) muscles.

and muscle atrophy, mainly in latissimus dorsi, triceps, and scapula alata muscles. We did not observe cranial nerve palsies, muscle pains, fasciculation, sensory disturbances, cerebellar ataxia, or abnormal deep tendon reflexes. Laboratory examinations revealed high serum levels of muscle-related enzymes (CK 10,779 mg/dL, aldolase 67.3 IU/L, and myoglobin 4,463 ng/mL), an elevated sedimentation rate (53 mm/h), anemia (10.3 g/dL), and liver dysfunction (aspartate transaminase, 272 U/L; alanine aminotransferase, 134 U/L; and lactate dehydrogenase, 1,617 U/L). The patient's renal function, glycometabolism, thyroidal function, lactic acid, and pyruvic acid were within the normal ranges. The patient was negative for autoimmune antibodies associated with myositis (including anti-Jo1 antibody, anti-nuclear antibody, and anti-mitochondrial antibody) and anti-neuritic antibodies. Viral antibodies against human t-cell leukemia virus type 1 and cytomegalovirus were also negative. Transthoracic cardiac echocardiography and electrocardiography revealed no abnormalities. A spirogram showed a normal vital capacity. Abdominal ultrasound showed solid echo findings on the posterolateral side of the bladder, and T2-weighted images on MRI showed an abnormal low signal mass lesion with an internally heterogeneous contrast effect upon T1 gadolinium enhancement, which suggested metastasis of uterine cancer (Fig. 1A and B). No abnormal lesions were seen on brain or spine MRI. Short tau inverted recovery images on muscle MRI revealed high-signal intensity lesions on the left side of the latissimus dorsi and triceps muscles (Fig. 1C-E). Nerve conduction studies showed no abnor-

malities, but a needle electromyographic study (EMG) showed myogenic patterns during voluntary movement on the left side of the upper extremities (1st dorsal interosseous and deltoid muscles). Based on these findings, a muscle biopsy from her left biceps muscle was performed. Hematoxylin and Eosin staining sections showed muscle fibers of various sizes accompanied by necrotic and regenerating fibers, and inflammatory cell infiltration (Fig. 2A and D). Muscle fiber immunostaining also showed the findings of myositis, including the co-localization of CD8 immunoreactivity (Fig. 2B) and major histocompatibility complex 1 (MHC-1) (Fig. 2C). On the other hand, the infiltration of macrophages (Fig. 2E) and a positive immunoreaction for HMGCR (Fig. 2F) colocalized with regenerating muscle fibers in H&E staining sections (Fig. 2D [arrow]) suggested IMNM. Furthermore, the patient's serum was positive for anti-HMGCR antibodies, but negative for anti-SRP antibodies. The patient was negative for anti-tumor antibodies (including Hu, Ri, and Yo antibodies). Based on these pathological findings and the additional serum examinations, she was diagnosed with anti-HMGCR-positive necrotic myopathy. The high serum level of CK spontaneously declined at rest after her admission, but her motor weakness did not improve, and her CK value remained in the range of 4,000-6,000.

Clinical course

The clinical course is shown in Fig. 3. Based on the pathological findings from the muscle biopsy, oral predniso-

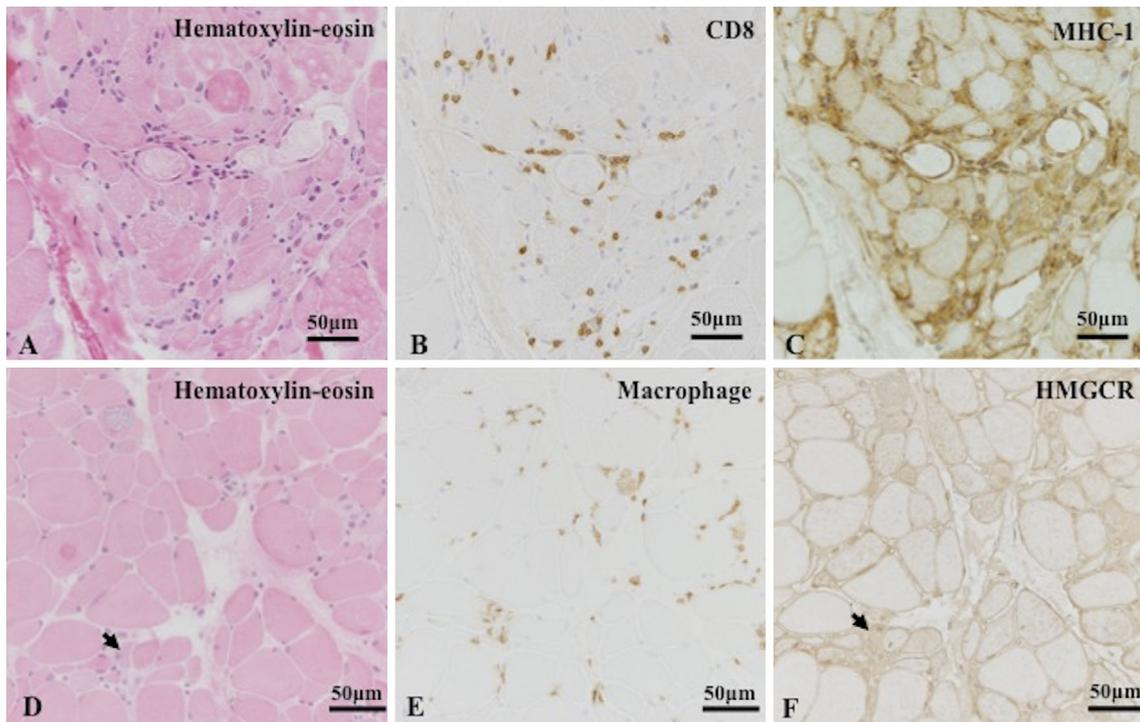


Figure 2. A, D: A Hematoxylin and Eosin (H&E) staining section of the left biceps shows various sizes of muscle fibers, with necrotic and regenerating fibers (A). B, C, E: Enzyme immunostaining revealed an increase in the expression of CD8-positive lymphocytes (B), MHC-I (C), and macrophages (E). F: Enzyme immunostaining revealed anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibody-positive fibers (arrow) colocalized with regenerating muscle fibers in an H&E staining section [D (arrow)].

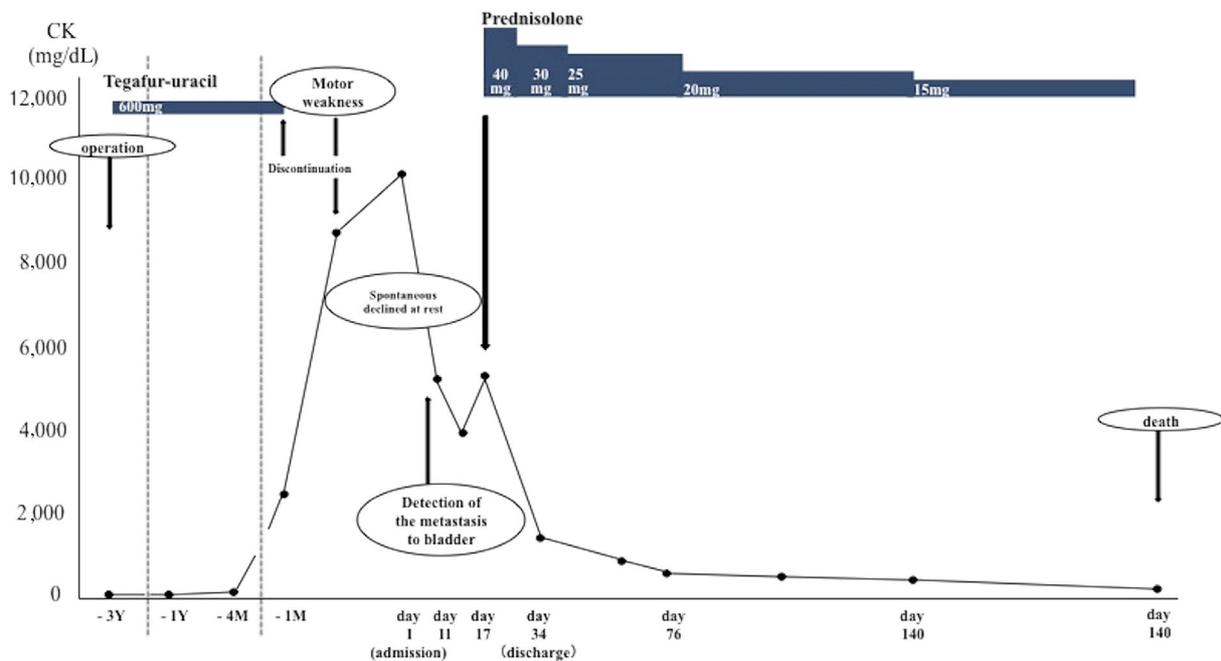


Figure 3. A high serum level of CK was detected at 3 years after the operation while the patient was receiving chemotherapy (tegafur-uracil). Her high serum level of CK continued even after the cessation of tegafur-uracil and motor weakness appeared. After admission, her high serum level of CK spontaneously declined at rest, but her motor weakness did not improve, and the CK value remained in the range of 4,000-6,000 mg/dL. Oral prednisolone was started at a dose of 40 mg/day. Her serum level of CK was reduced and her clinical symptoms gradually improved during steroid therapy. No relapse occurred during the tapering of prednisolone.

lone was initiated at a dose of 40 mg/day. Her high serum level of CK was reduced and her clinical symptoms gradually improved. No relapse occurred during the tapering of the prednisolone dose; however, she died approximately 4 months after discharge due to bleeding from the invasion site in the bladder.

Discussion

IMNM with anti-HMGCR antibodies is rare and accounts for 12-22% of IMNM cases (4, 7). It has been proposed that anti-HMGCR antibodies are induced by the combination of MHC-1 and HMGCR antigens in patients taking statins (9); this in turn leads to an increase in the expression of HMGCR in the regenerating muscle (2). However, anti-HMGCR antibodies have been detected in patients with malignancies or collagen disease (e.g., polymyositis, dermatomyositis, and scleroderma) (5-7), and their relationship with these diseases is unclear. Alshehri et al. (6) and Watanabe et al. (7) reported that IMNM with anti-HMGCR antibodies was present in 4-10% of patients with malignancies, but did not present pathological evidence to support a paraneoplastic mechanism.

The pathological findings of anti-HMGCR antibody-positive IMNM have been reported to include necrotic muscle fibers without significant inflammatory cell infiltration (2). Our case showed atypical findings of anti-HMGCR antibody-positive IMNM with respect to inflammatory cell infiltration. Furthermore, there were no other factors to explain the inflammatory change, with the exception of the paraneoplastic factor-specifically, invasion of the bladder due to metastasis from uterine cancer. Furthermore, we observed an increase in the expression of CD8-positive lymphocytes, which might indicate a role of tumor immunity in myocyte disruption (10). This overexpression of CD8-positive lymphocytes around non-necrotic MHC-1 positive muscle fibers was also reported as a typical finding of myositis (11). Aside from these findings, positive HMGCR immunostaining of necrotic and regenerating muscle fibers with infiltration by macrophages, which were observed in our patient, could indicate the involvement of necrotic myopathy. With regard to the relationship between cancer and HMGCR, Gustbee et al. (12) reported the overexpression of HMGCR in tumor tissue, and Stine et al. (13) reported the therapeutic effects of statins in patients with malignancies. Hence, the increased expression of HMGCR may be associated with malignancy, and could lead to appearance of anti-HMGCR antibodies. Furthermore, we considered that the myositis-like findings, in addition to the findings of IMNM, might be associated with the paraneoplastic mechanism; however, the reason was not clear.

In conclusion, we reported a suspected case of paraneo-

plastic anti-HMGCR antibody-positive IMNM. We suggest that the pathogenesis of IMNM may include not only drug-induced cases, but also malignant tumors.

The authors state that they have no Conflict of Interest (COI).

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