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HMGR ANTIBODY-ASSOCIATED MYOPATHY AS A PARANEOPLASTIC MANIFESTATION OF ESOPHAGEAL CARCINOMA

Immune-mediated myopathies with antibodies may be triggered by statin exposure, but some patients with these disorders are statin-naïve; thus, there are probably other etiologies.¹ Several malignant tumors, including esophageal squamous cell carcinoma (ESCC), overexpress 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) protein.² To date, the relationship between anti-HMGR antibody-associated myopathy (HMGR-M) and malignancy remains unclear.^{3,4} Here, we report a case of HMGR-M in a patient with ESCC and paraneoplastic syndrome.

Case report. A 59-year-old Japanese man was admitted to our hospital because of progressive proximal muscle weakness. He had a history of smoking and excessive alcohol consumption. He had no remarkable medical history and took no medications including statins. Six months before this admission, he noted difficulty raising his arms, and then had gradually deteriorating muscle weakness and finally difficulty walking. On neurologic examination, we observed mild muscle weakness in the patient's proximal limbs. We also noted muscle atrophy in the patient's shoulder girdle and upper limbs, but with normal cranial nerves, sensation, coordination, and reflexes.

Laboratory results showed elevated serum creatine kinase (CK) levels (9,057 IU/L; normal, 45–163 IU/L) and elevated serum anti-HMGR antibodies measured using antigen-capture ELISA (appendix e-1 on the *Neurology*® Web site at Neurology.org; 9.0 units [using 4.3 units as the cutoff]),⁵ but negative results for other myositis-specific autoantibodies. The patient's leukocytes did not express human leukocyte antigen-DR11 antigen, which is known as a genetic risk factor for HMGR-M.⁴ Needle EMG showed active myogenic changes in the deltoid and biceps muscles.

Muscle biopsy of the left biceps muscle revealed perimysial and endomysial mononuclear cell infiltrates, necrosis, variability in fiber size, and an increase in perimysial connective tissue (figure 1A). Muscle fibers expressed major histocompatibility complex (MHC) class I. We also observed CD8-positive T-lymphocytes and CD68-positive macrophages (figure 1, B and C).

Based on these findings, we diagnosed the patient with HMGR-M.

After hospitalization, the patient's muscle weakness worsened. We investigated further to rule out malignancy, and found ESCC on gastrointestinal endoscopy and biopsy. Chest CT showed lymph node metastasis. The patient underwent subtotal esophagectomy with 2-field lymphadenectomy on day 38 following admission. Pathology staging showed T1N3M0, stage IIIC according to the seventh edition of the Union for International Cancer Control tumor node metastasis staging system. Immunohistochemistry and immunoblotting revealed increased HMGR expression in the patient's muscle and ESCC tissues (figure 1, D, E, and H–K, and figure e-1). We observed a similar ratio of CD8-positive cells and CD68-positive cells in the patient's muscle and ESCC tissue (figure 1, B, C, F and G, and figure e-2).

The patient's clinical course is illustrated in figure 1L. After tumor resection, we treated him with IV immunoglobulin, methylprednisolone, and azathioprine. Serum CK levels decreased, and then muscle strength gradually improved. Serum anti-HMGR antibody levels first increased and then decreased after ESCC resection. However, levels increased again upon recurrence of lymph node metastasis. The patient then underwent chemotherapy with cisplatin and 5-fluorouracil, but the metastasis progressed. He was transferred to a palliative care facility on day 255 following admission.

Discussion. Anti-HMGR antibodies may be seen in patients with myopathy, but have not been intensively studied in patients with malignancy. We observed decreased serum anti-HMGR antibody levels after ESCC resection, which then increased with ESCC recurrence. Oncogene MYC positively regulates HMGR expression.² These findings suggest that serum anti-HMGR antibody levels reflect the progression of ESCC.

The patient's muscle had immunohistochemical features characteristic of HMGR-M, with prevalent macrophages.⁶ In addition, the predominance of cytotoxic T-cells and myofiber MHC class I expression indicated an underlying cell-mediated autoimmune mechanism for the inflammation.

Autoantigen expression is often increased in regenerating muscle cells in patients with myositis including those with HMGR-M.¹ One possible pathomechanism

Supplemental data
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Figure 1 Pathologic features, immunoblot analysis, and clinical course

Hematoxylin & eosin (H&E) staining of the patient's biceps muscle (MB15-35) (A); anti-CD8 (B) and CD68 (C) immunohistochemistry (IHC) of MB15-35; anti-3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGR) IHC of the patient's muscle (MB15-35) (D) and a disease control (MB15-54) with myopathy with anti-jo-1 antibody (E); anti-CD8 (F) and CD68 (G) IHC of the patient's esophageal squamous cell carcinoma (ESCC) tissue; anti-HMGR IHC of ESCC tissue (H) and surrounding normal esophageal tissue (I); immunoblot analysis of muscle (J) and esophageal tissue (K) from the patient. We compared HMGR expression in the muscle of MB15-35 with that of a healthy subject (P1234171, purchased from BCH Research, Cheshire, UK) and in disease control subjects: MB15-15 with myopathy with anti-mitochondrial antibody, MB15-23 with myopathy with anti-signal recognition particle antibody, and MB15-54. We used GAPDH as internal control for protein loading. (L) Clinical course. Ab = antibody; CK = creatine kinase; IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; MRC = Medical Research Council; PSL = prednisolone. Bars: 50 μ m for A, B, C, D, E, F, and G, and 10 μ m for H and I.

of paraneoplastic myositis is that of an autoimmune response against cancer crossreacting with regenerating muscle cells, and a subsequent feed-forward loop of tissue damage and antigen selection leading to cytotoxic T-cell

response and further muscular damage.⁷ It is plausible that anti-HMGR antibodies play an important role in this cross-reaction. If so, suppression of the secondary cytotoxic T-cell response with immunosuppressive

therapies might result in improved muscle strength without reducing serum anti-HMGCR antibody levels, as seen in our case.

HMGCR-M can be a clinical manifestation of a paraneoplastic syndrome in patients with ESCC. Although a definitive link between malignancy and HMGCR-M has not been established, our case suggests that a comprehensive malignancy screen should be considered in patients with HMGCR-M with no known statin exposure.

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Author contributions: K.T.: study design and concept, data acquisition, analysis and interpretation, drafting the manuscript. K.H.: analysis and interpretation, data acquisition. Y.M.: analysis and interpretation, data acquisition, critical manuscript revision. H.N.: analysis and interpretation, data acquisition. Y.N.: analysis and interpretation, data acquisition. M. Koike: analysis and interpretation, data acquisition. S.N.: analysis and interpretation, data acquisition. Y.R.: analysis and interpretation, data acquisition. K.S.: analysis and interpretation, data acquisition, manuscript revisions. N.A.: analysis and interpretation, data acquisition, manuscript revision. M.I.: analysis and interpretation, data acquisition. Y.S.: analysis and interpretation, data acquisition. M.A.: analysis and interpretation, data acquisition. M. Katsuno: study supervision, critical manuscript revisions, data interpretation, study design and concept.

Study funding: Supported by KAKENHI grants from MEXT/JSPS, Japan (no. 26293206, 15K15337).

Disclosure: K. Tsujikawa reports no disclosures relevant to the manuscript. K. Hara is supported by KAKENHI Grant-in-Aid for Young Scientists B from JSPS, Japan (No. 15K1984). Y. Muro serves as an editorial board member of Immunopharmacology and Immunotoxicology and the Open Rheumatology Journal. He is supported by KAKENHI Grant-in-Aid for Scientific Research C from JSPS, Japan (No. 26461656). H. Nakanishi reports no disclosures relevant to the manuscript. Y. Niwa is supported by KAKENHI Grant-in-Aid for Young Scientists B from JSPS, Japan (No. 15K19878). M. Koike and S. Noda report no disclosures relevant to the manuscript. Y. Riku is supported by KAKENHI Grant-in-Aid for Young Scientists B from JSPS, Japan (No. 15K19483) and a grant from the Nitto Foundation. K. Sahashi is supported by KAKENHI Grant-in-Aid for Scientific

Research C from JSPS, Japan (No. 26461268). N. Atsuta is supported by KAKENHI Grant-in-Aid for Scientific Research C from JSPS, Japan (No. 25461277). M. Ito is supported by KAKENHI Grant-in-Aid for Scientific Research C from JSPS, Japan (No. 25461313). Y. Shimoyama reports no disclosures relevant to the manuscript. M. Akiyama serves as a section editor of Journal of Dermatological Science and the Journal of Dermatology. He is supported by KAKENHI Grant-in-Aid for Scientific Research B from JSPS, Japan (No. 15H04887). M. Katsuno is supported by KAKENHI grants from JSPS, Japan (No. 26293206, 15K15337); a grant from Japan Agency for Medical Research and Development (No. 15ek0109025); and a grant from the Daiichi Sankyo Foundation of Life Science. Go to Neurology.org for full disclosures.

Received December 26, 2015. Accepted in final form May 9, 2016.

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DIFFUSION-WEIGHTED MRI ABNORMALITIES ANTEDATE THE ONSET OF SPORADIC CREUTZFELDT-JAKOB DISEASE

Sporadic Creutzfeldt-Jakob disease (sCJD) is a fatal progressive neurodegenerative disease that presents with progressive dementia and is accompanied by behavioral and psychiatric features and myoclonus. Multimodal approaches, such as EEG, diffusion-weighted imaging (DWI) of brain MRI, and CSF examinations, have been applied to increase the diagnostic accuracy of sCJD. Previous studies have suggested that DWI MRI could be the most useful modality for sCJD diagnosis.^{1–3} Recently, a study that compared MRI and pathologic findings demonstrated that DWI signal changes

correlated with the disease duration and the histopathologic degree of spongiosis.⁴ However, when DWI signal changes emerge during the prodromal or incipient phase of sCJD remains unclear. Here, we present serial MRI findings acquired from a patient with sCJD before and after the onset of clinical symptoms, demonstrating that the emergence of unilateral cortical hyperintensity on DWI antedates the onset of sCJD.

Case report. A 69-year-old man was referred to our Department at the end of January 2013, because of an inability to perform daily activities, including driving and toileting, due to progressive dementia over a 4-month period. The patient had been regularly