Cancer association as a risk factor for anti-HMGCR antibody-positive myopathy

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ABSTRACT

Objective: To show cancer association is a risk factor other than statin exposure for anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody-positive (anti-HMGCR Ab+) myopathy.

Methods: We analyzed the clinical features and courses of 33 patients (23 female and 10 male) with anti-HMGCR Ab+ myopathy among 621 consecutive patients with idiopathic inflammatory myopathies.

Results: Among the 33 patients, 7 (21%) were statin-exposed and 26 were statin-naïve. In relation with cancer, there were 12 patients (statin-exposed, $n = 4$) with cancers detected within 3 years of myopathy diagnosis (cancer association), 3 patients (all statin-naïve) with cancers detected more than 3 years before myopathy diagnosis (cancer history), 10 cancer-free patients followed up for more than 3 years (all statin-naïve), and 8 patients without cancer detection but followed up for less than 3 years (statin-exposed, $n = 3$). Therefore, 12 patients with cancer association (36%) formed a larger group than that of 7 statin-exposed patients (21%). Among 12 patients with cancer association, 92% had cancer detection within 1 year of myopathy diagnosis (after 1.3 years in the remaining patient), 83% had advanced cancers, and 75% died of cancers within 2.7 years. Of interest, 1 patient with cancer history had sustained increase in creatine kinase level over 12 years from cancer removal to the development of weakness.

Conclusions: Patients with cancer association formed a large group with poor prognosis in our series of patients with anti-HMGCR Ab+ myopathy. The close synchronous occurrence of cancers and myopathies suggested that cancer association is one of the risk factors for developing anti-HMGCR Ab+ myopathy. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e290; doi: 10.1212/NXI.0000000000000290

GLOSSARY

Ab = antibodies; **CAM** = cancer-associated myositis; **CI** = confidence interval; **CK** = creatine kinase; **CS** = corticosteroid; **DM** = dermatomyositis; **ENMC** = European Neuromuscular Centre; **HMGCR Ab** = 3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody; **IIM** = idiopathic inflammatory myopathy; **IVIg** = IV immunoglobulin; **MHC** = major histocompatibility complex; **mRS** = modified Rankin Scale; **MSA** = myositis-specific antibody; **MTX** = methotrexate; **N/R** = necrotic/regenerating; **NAM** = necrotizing autoimmune myopathy; **NSM** = nonspecific myositis; **SIR** = standardized incidence ratio; **SRP** = signal recognition particle.

Idiopathic inflammatory myopathies (IIMs) are characterized by clinical features, myositis-specific antibodies (MSAs), and pathologic findings. Among MSAs, the anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody (anti-HMGCR Ab) was initially found as an MSA strongly associated with statin exposure.^{1–3} Subsequent studies^{4–10} showed various prevalence rates of statin exposure in anti-HMGCR Ab+ myopathy, which were reportedly low in Asian countries.^{7,8,10} The pathogenesis of anti-HMGCR Ab+ myopathy has been unknown. However, the genetic

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susceptibility of patients, environmental triggers including statin exposure, or unknown factors have been suggested to be important.^{11,12}

Recently, increased risk of cancer in patients with anti-HMGCR Ab+ necrotizing autoimmune myopathy (NAM) has been reported.¹³ There is also a recent report showing a trend toward increased prevalence of anti-HMGCR Ab among patients with IIM with cancers.⁹ We also showed in our previous study that anti-HMGCR Ab was the second most frequent autoantibody in 75 patients with cancer-associated myositis (CAM).¹⁴ However, in that study, we did not find a significantly increased prevalence rate of anti-HMGCR Ab among patients with CAM, because of a considerable number of cancer-free patients with anti-HMGCR Ab+ myopathy presumably related to statin exposure or other risk factors, which we did not analyze in that study. Therefore, we considered it important to analyze the clinical courses of patients with anti-HMGCR Ab+ myopathy in relation to statin exposure and cancer development in larger series of patients. Our aim was to show that cancer association becomes a risk factor other than statin exposure for anti-HMGCR Ab+ myopathy.

METHODS Patients. We screened 621 consecutive adult patients with IIM (16 years or older) who were pathologically diagnosed in the University of Tokyo Hospital between 2000 and 2015 and whose serum samples at biopsy were available. In screening, patients with sporadic inclusion body myositis or sarcoid myopathy were excluded on the basis of clinical and pathologic findings. Clinical information was retrospectively analyzed by reviewing the patients' clinical records. The disease onset was defined as the initial awareness of muscular symptoms or the detection of elevated serum creatine kinase (CK) level. The disease duration was defined as the duration between the time of disease onset and muscle biopsy for histopathologic diagnosis.

Definition of the association with cancers. With regard to the association with cancers, we defined patients with cancer association as patients with cancers detected within 3 years of myopathy diagnosis on the basis of commonly used criterion for CAM,^{15,16} and patients with cancer history as patients in whom cancers were detected but more than 3 years before the time of myopathy diagnosis. Among the patients in whom cancers were not detected, we defined cancer-free patients as patients without cancer detection who were followed up for more than 3 years after myopathy diagnosis.

Detection of anti-HMGCR Ab and other MSAs. For the detection of anti-HMGCR Ab, we performed ELISA, as reported elsewhere.¹⁴ In patients found to be positive by ELISA, we additionally performed Western blot analysis (figure e-1 at Neurology.org/nn). The patients with positive results in both methods were determined to be positive for anti-HMGCR Ab. The patients who were positive for anti-HMGCR Ab were

screened for other MSAs, including anti-Jo-1, anti-PL-7, anti-PL-12, and anti-Mi-2 Abs by dot-blot analysis (DirecT AG, Freiburg im Breisgau, Germany), anti-signal recognition particle (SRP) antibodies (Ab) by RNA immunoprecipitation assay (Health Sciences Research Institute, Kanagawa, Japan), and anti-transcriptional intermediary factor 1- γ Ab by protein-immunoprecipitation assay.¹⁴

Histochemical and immunohistochemical evaluations.

Cryostat sections of rapidly frozen muscle specimens were processed for routine histochemistry and immunohistochemistry. Anti-human major histocompatibility complex (MHC) Class I/Class II antibodies and anti-C5b-9 antibodies (DAKO, Carpinteria, CA) were used as primary antibodies in immunohistochemical stains. The amount of necrotic/regenerating (N/R) fibers and inflammatory cell infiltration were semiquantitatively estimated: 1 = absent to mild; 2 = moderate; 3 = severe. We defined NAM pathology as having the histopathologic findings of N/R fibers ≥ 2 and inflammatory cell infiltration ≤ 1 on the basis of the criteria established by the European Neuromuscular Centre (ENMC).¹⁷ The extent of MHC Class I or Class II antigen expression on non-necrotic fibers (over 25% of fibers per section) and C5b-9 deposition on sarcolemma (1 or more non-necrotic fibers) were also recorded.

Statistical analysis. A 2-tailed Mann-Whitney *U* test was performed for different sets of continuous data of clinical features and Fisher exact test was used to compare categorical data. A *p* value of less than 0.05 was considered to indicate statistical significance. Statistical calculations were performed using JMP Pro 11 (SAS Institute, Cary, NC).

The risk of cancer was estimated by using the standardized incidence ratio (SIR), the ratio of the observed to expected numbers of cancer, and its 95% confidence interval (CI) assuming that the observed number of cases followed a Poisson distribution. In the present analysis, the observed numbers of cancer were compared with those expected to occur in the general population, adjusted for the same age and sex structure, on the basis of the incidence rates of cancer in 2008 provided by Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan (ganjoho.jp/reg_stat/statistics/dl/index.html). Two types of SIRs were estimated: (1) the SIR of cancers within 3 years of myopathy diagnosis (6 years in total), as reported in a recent study,¹³ where the patients who died, dropped out from follow-up, or had cancer detection during 6 years around myopathy diagnosis were censored at the date of death, last visit, or cancer detection, and the patients with cancers detected more than 3 years before myopathy diagnosis were excluded; and (2) the SIR of cancers within 1 year of myopathy diagnosis (2 years in total), using the same methodology.

Standard protocol approvals, registrations, and patient consent.

This study was approved by the internal review boards of the University of Tokyo and National Defense Medical College. From each patient, written informed consent was obtained at the time of biopsy and serum sampling.

RESULTS Anti-HMGCR antibodies in patients with IIMs. Thirty-three of 621 sera (5.3%) from patients with IIMs showed positivity for anti-HMGCR Ab in both ELISA and Western blot analysis (figure e-1).

Characteristics of anti-HMGCR Ab+ myopathy patients in relation to cancers. Table 1 shows clinical and pathologic features of patients with anti-HMGCR Ab+ myopathies. Thirty-three patients with anti-HMGCR Ab myopathies consisted of 23 women and 10 men.

The age at disease onset was 59 ± 15 years. One woman developed myopathy at 9 months of pregnancy. The associated diseases or factors were as follows: statin exposure ($n = 7$, 21%), rheumatoid arthritis ($n = 2$, 6%), chronic hepatitis C virus infection ($n = 2$, 6%), cancer association ($n = 12$, 36%), and cancer history ($n = 3$, 9%). The statins administered in 7 statin-exposed patients were atorvastatin ($n = 3$), simvastatin ($n = 2$), pitavastatin ($n = 1$), and rosuvastatin ($n = 1$). The average onset age in statin-naïve patients (56 ± 16 years) was younger than that in statin-exposed patients (71 ± 8 years) ($p = 0.03$).

On the basis of the ENMC criteria,¹⁷ 32 patients were classified to have NAM ($n = 21$, 66%), non-specific myositis (NSM) ($n = 9$, 28%), and dermatomyositis (DM) ($n = 2$, 6%). One patient was not classified because the biopsied sample was not suitable for assessment (only fatty tissue was observed).

In relation to cancer, 33 patients were classified as follows: 12 patients with cancer association (36%), 3 patients with cancer history (9%), 10 cancer-free patients (30%), and 8 patients (24%) without cancers but followed up for less than 3 years. Among them, statin exposure was found in 4 of 12 (33%) patients with cancer association, 3 of 8 (38%) patients without cancers but followed up for less than 3 years, and none of the patients was statin-exposed in 3 patients with cancer history and 10 cancer-free patients. Therefore, among 33 patients with anti-HMGCR Ab+ myopathy, the 12 patients with cancer association (36%) formed a larger group than that of 7 patients with statin exposure (21%) in our series (4 patients had both cancer association and statin exposure). In comparison of the characteristics between 12 patients with cancer association and 10 cancer-free patients, patients with cancer association were older at onset ($p = 0.01$) with frequent myalgia ($p = 0.03$), higher C-reactive protein levels and erythrocyte sedimentation rate ($p = 0.03$ and 0.03), and much higher mortality rate in prognosis ($p < 0.001$) compared with cancer-free patients. In comparison of pathologic findings in relation to cancer association, there were no differences between 12 patients with cancer association and 10 cancer-free patients.

Clinical courses of patients with anti-HMGCR Ab+ myopathy with cancers. Figure 1 (upper half part) shows the follow-up periods of 12 patients with cancer association and 3 patients with cancer history in relation with cancer detection and statin exposure. In 12 patients with cancer association, 92% (11/12) of the cancers were detected within 1 year of myopathy diagnosis, and the remaining one was detected 1.3 years after myopathy diagnosis. In the analysis of the risk of cancer, the SIR of cancers within 3 years of myopathy diagnosis was 9.1 (95% CI 4.5–16.2), and

that of cancers within 1 year of myopathy diagnosis was 22.1 (95% CI 10.6–40.7). In 3 patients with cancer history, 2 patients had early colon cancers 11 or 12 years before myopathy diagnosis and 1 patient had lymphoma 7 years before myopathy diagnosis. All 3 patients were followed with no signs of cancer recurrence.

Table 2 shows a summary of the clinical courses of 12 patients with cancer association (patients 1–12) and 3 patients with cancer history (patients 13–15). The 12 patients with cancer association were classified into those with NAM ($n = 8$), NSM ($n = 3$), and DM ($n = 1$). The original cancer sites varied among patients; however, 83% ($n = 10$) of the cancers were detected at an advanced stage. Regarding their clinical courses, 9 patients (75%) died of cancers between 0.2 and 2.7 years after myopathy diagnosis (1.2 ± 1.0 years, within 1 year in 6 patients).

For the treatment of 12 patients with cancers, 9 patients received anticancer treatments (surgical resection, $n = 5$; chemotherapy, $n = 5$; radiation, $n = 4$; more than one therapy, $n = 4$) and 3 patients were followed with palliative care. For the treatment of myopathy, oral corticosteroid (CS) was introduced in all 12 patients (40–100 mg/d), in combination with other immunosuppressive or immunomodulating agents in 7 patients (patients 1, 5–7, 9–11) (table 2). Three patients whose cancers were surgically removed and being without relapses at this moment (patients 1–3) achieved normalization of CK level with improvement of muscle strength at last follow-up. Six patients who died of cancers within 1 year of myopathy diagnosis (patients 4–6, 9–11) showed worsening of general status including muscle strength along with cancer progression and it was difficult to assess the effects of immunotherapy. Three patients who died of cancers more than 2 years after myopathy diagnosis (patients 7, 8, 12) had periods showing decrease in serum CK level and improvement of muscle strength to some extent, however, muscle strength re worsened along with cancer progression.

The 3 patients with cancer history were classified into those with NSM ($n = 2$) and NAM ($n = 1$). Regarding treatments for myopathies, all 3 patients required IV immunoglobulin (IVIg) therapy in addition to other immunosuppressive treatments. At last visit, 2 patients (patients 13, 14) were under good control with normalization of their muscle strength. However, the remaining patient (patient 15) still had severe disability of daily living despite the normalization of CK level at last visit. Of interest, one man (patient 13), in whom increased serum CK level was initially detected at the same time as the surgical removal of colon cancer, showed a sustained increase in CK level ($>1,000$ IU/L) over 12 years. He had been followed up as having idiopathic hyperCKemia until the development of mild weakness in his lower

Table 1 Clinical and pathologic features of patients with anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody myopathy

Clinical and pathologic findings	All patients (n = 33)	Patients with cancer association (n = 12) ^a	Patients with cancer history (n = 3) ^b	Cancer-free patients (n = 10) ^{c,d}	Patients without cancer followed <3 years (n = 8)	Patients with cancer association (n = 12) vs cancer-free patients (n = 10), p value ^{e,f}
Male:female	10:23	2:10	2:1	3:7	3:5	0.62
Age at disease onset, y	59 ± 15	65 ± 12	50 ± 7	49 ± 14	68 ± 16	0.01
Associated disorders						
Cancer	15/33 (45)	12/12 (100)	3/3 (100)	0/10 (0)	0/8 (0)	—
Within 3 years of myopathy diagnosis	12/33 (36)	12/12 (100)	0/3 (0)	0/10 (0)	0/8 (0)	—
Statin exposure	7/33 (21)	4/12 (33)	0/3 (0)	0/10 (0)	3/8 (38)	0.10
Collagen disease	2/33 (6)	1/12 (8)	0/3 (0)	1/10 (10)	0/8 (0)	1.00
Chronic hepatitis C virus infection	2/33 (6)	0/12 (0)	0/3 (0)	1/10 (10)	1/8 (13)	0.45
Classification by ENMC^d						
Necrotizing autoimmune myopathy	21/32 (66)	8/12 (67)	1/3 (33)	6/9 (67)	6/8 (75)	1.00
Nonspecific myositis	9/32 (28)	3/12 (25)	2/3 (67)	2/9 (22)	2/8 (25)	1.00
Dermatomyositis	2/32 (6)	1/12 (8)	0/3 (0)	1/9 (11)	0/8 (0)	1.00
Clinical signs and symptoms						
Chronic progression (>1 year)	5/33 (15)	2/12 (17)	1/3 (33)	2/10 (20)	0/8 (0)	1.00
Asymptomatic hyperCKemia (>1 year)	4/33 (12)	1/12 (8)	1/3 (33)	2/10 (20)	0/8 (0)	0.57
Severe muscle weakness (MRC ≤3) ^g	25/33 (76)	10/12 (83)	1/3 (33)	8/10 (80)	6/8 (75)	1.00
Myalgia	14/33 (42)	7/12 (58)	1/3 (33)	1/10 (10)	5/8 (63)	0.03
Dysphagia	8/33 (24)	5/12 (42)	0/3 (0)	1/10 (10)	2/8 (25)	0.16
Skin rash ^h	5/33 (15)	3/12 (25)	0/3 (0)	1/10 (10)	1/8 (13)	0.59
Arthralgia	2/33 (6)	0/12 (0)	1/3 (33)	1/10 (10)	0/8 (0)	0.45
Interstitial lung disease	1/33 (3)	0/12 (0)	0/3 (0)	1/10 (10)	0/8 (0)	0.45
Modified Rankin Scale	2.6 ± 1.0	2.6 ± 0.8	1.7 ± 0.6	2.5 ± 0.8	3.0 ± 1.2	0.80
Laboratory data						
CK level, IU/L	9,767 ± 8,131	12,094 ± 12,040	11,006 ± 10,861	8,361 ± 3,459	7,569 ± 2,661	0.77
CRP level, mg/dL	2.1 ± 5.1	4.2 ± 7.8	1.2 ± 2.0	0.1 ± 0.1	1.9 ± 3.2	0.03
ESR, mm/h	28.2 ± 25.8	38.1 ± 22.2	14.3 ± 6.4	15.1 ± 15.1	39.3 ± 45.0	0.03
Antinuclear antibodies (≥1:40)	9/30 (30)	2/10 (20)	1/3 (33)	3/10 (30)	3/7 (43)	1.00
Myositis-specific autoantibodies ⁱ	2/33 (6)	0/12 (0)	1/3 (33)	1/10 (10)	0/8 (0)	0.45
Mortality rate during follow-up	9/33 (21)	9/12 (75)	0/3 (0)	0/10 (0)	0/8 (0)	<0.001

Continued

Table 1 Continued

Clinical and pathologic findings	All patients (n = 33)	Patients with cancer association (n = 12) ^a	Patients with cancer history (n = 3) ^b	Cancer-free patients (n = 10) ^{c,d}	Patients without cancer followed <3 years (n = 8)	Patients with cancer association (n = 12) vs cancer-free patients (n = 10), p value ^{e,f}
Pathologic findings^d						
N/R fibers						
Absent to mild	1/32 (3)	1/12 (8)	0/3 (0)	0/9 (0)	0/8 (0)	1.00
Moderate	8/32 (25)	3/12 (25)	2/3 (67)	2/9 (22)	1/8 (13)	1.00
Severe	23/32 (72)	8/12 (67)	1/3 (33)	7/9 (78)	7/8 (88)	0.66
Inflammation						
Absent to mild	24/32 (75)	10/12 (83)	1/3 (33)	7/9 (78)	6/8 (75)	1.00
Moderate	6/32 (19)	1/12 (8)	2/3 (67)	2/9 (22)	1/8 (13)	0.55
Severe	2/32 (6)	1/12 (8)	0/3 (0)	0/9 (0)	1/8 (13)	1.00
MHC Class I expression	16/32 (50)	5/12 (42)	1/3 (33)	6/9 (67)	4/8 (50)	0.39
MHC Class II expression	0/0 (0)	0/0 (0)	0/0 (0)	0/0 (0)	0/0 (0)	—
C5b-9 deposition on sarcolemma	23/32 (72)	6/12 (50)	2/3 (67)	8/9 (89)	7/8 (88)	0.16

Abbreviations: CK = creatine kinase; CRP = C-reactive protein; ENMC = European Neuromuscular Centre; ESR = erythrocyte sedimentation rate; MHC = major histocompatibility complex; MRC = Medical Research Council; N/R fibers = necrotic/regenerating fibers.

Values are mean ± SD or n (%).

^aPatients with cancer association = patients with cancers detected within 3 years of myopathy diagnosis.

^bPatients with cancer history = patients in whom cancers were detected but more than 3 years before the time of myopathy diagnosis.

^cCancer-free patients = patients without cancer detection who were followed up for more than 3 years after myopathy diagnosis.

^dOne patient was not classified because the biopsied sample was not suitable for assessment (only fatty tissue without muscle fibers).

^eThere were also no significant differences in the pathologic findings between 11 patients with cancers detected within 1 year of myopathy diagnosis and 10 cancer-free patients (data not shown).

^fA p value of less than 0.05 was considered to indicate statistical significance.

^gMuscle weakness was proximal dominant and symmetrical in all patients. The weakest muscle strength of the neck or extremities was evaluated.

^hTwo patients had typical dermatomyositis rash.

ⁱAnti-Jo-1, anti-PL-7, anti-PL-12, anti-Mi-2, anti-signal recognition particle (SRP), and anti-transcriptional intermediary factor 1-γ antibodies were examined. Anti-SRP antibodies were positive in 2 patients (6%), whereas other myositis-specific antibodies were not detected.

Figure 1 Follow-up periods of 33 anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody (HMGCR Ab+) myopathy patients in relation to cancer or statin exposure

The upper half shows the follow-up periods of 12 patients with cancer association (statin-exposed, $n = 4$) and 3 patients with cancer history. In 12 patients with cancer association, 92% (11/12) of the cancers were detected within 1 year of myopathy diagnosis (the remaining one was detected 1.3 years after myopathy diagnosis), and 75% (9/12) died of cancers between 0.2 and 2.7 years after myopathy diagnosis. All 3 patients with cancer history had their cancers treated (closed triangles) and showed no signs of cancer recurrence during follow-up. The lower half shows the follow-up periods of 18 anti-HMGCR Ab+ myopathy patients without cancer (statin-exposed, $n = 3$). Among them, 10 patients were followed up for more than 3 years after myopathy diagnosis and regarded as cancer-free patients. Closed circles = cancers associated with myopathies detected within 3 years of myopathy diagnosis; closed triangles = past cancers detected and treated more than 3 years before myopathy diagnosis with no signs of recurrence in follow-up periods.

limbs. In the remaining 2 patients with cancer history (patients 14, 15), detailed information on their serum CK levels prior to the onset of muscular symptoms was unavailable.

Clinical courses of patients with anti-HMGCR Ab+ myopathy without cancer. Among 18 patients without cancer (figure 1, lower half part), 10 patients were followed up for more than 3 years after myopathy diagnosis (5.7 ± 2.9 years; range 3.1–10.7) and regarded as cancer-free.

Table 3 shows a summary of the clinical courses of 10 cancer-free patients. The 10 patients were classified into those with NAM ($n = 6$), NSM ($n = 2$), DM ($n = 1$), and unclassified (fatty tissue, $n = 1$). All the patients were statin-naïve. Although immunotherapy for myopathy was introduced individually by physicians in charge, all but one patient required additional immunosuppressive treatments other than steroids. During clinical courses, immunosuppressants were administered at the initial part of the treatments in combination with steroids in 6 patients (patients 2, 4–6, 9, 10) or at the time of exacerbation

in 3 patients (patients 1, 7, 8). IVIg therapy was introduced at the initial part of the treatments in 5 patients (patients 1, 2, 8–10) and repeated at the time of exacerbation in 3 patients (patients 8–10). After IVIg therapy, all patients showed improvement of muscle strength and decrease in CK level. At last visit, 10 patients were treated with CS alone ($n = 5$), CS with immunosuppressants (methotrexate [MTX], $n = 3$; azathioprine, $n = 1$), or MTX alone ($n = 1$).

At last visit, 5 patients (patients 1–5) showed normalization of CK levels with no significant or slight disability (modified Rankin Scale [mRS] 1 or 2). In contrast, the remaining 5 patients (patients 6–10) showed sustained increase in CK level, including 2 patients (patients 6, 7) with moderate or moderately severe disability (mRS 3 or 4) and increased CK levels. Interestingly, 3 patients (patients 8–10) showed no or slight muscular symptoms (mRS 0 or 1) despite markedly increased CK levels at last visits ($2,871 \pm 1,152$ IU/L; range 1,701–4,004). These 3 patients developed myopathy at relatively younger ages. Although they showed resistance to combined treatments with steroids and immunosuppressants, IVIg

Table 2 Clinical courses of patients with anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody myopathy with cancer association or cancer history

Patient	Onset age, y/sex	Statin exposure	Other MSAs	Classification by ENMC	Cancer		Pretreatment			Treatment		Follow-up period, y ^a	Clinical outcome (mRS)
					Site (stage)	Time between cancer and myopathy, y	MRC, UE/LE	mRS	CK, IU/L	Cancer therapy	Myopathy therapy		
1	34/M ^b	—	—	DM	Lymphoepithelial, thyroid (unclassified)	−0.1	2/3	3	46,466	Surgery, Rad	CS, MP, IVIg	0.4	3
2	77/F	—	—	NSM	Gastric (advanced)	−0.2	4/3	3	5,180	Surgery	CS	1.5	1
3	78/F	—	—	NSM	Ovary (early)	−0.1	4/4	2	3,831	Surgery	CS	3.4	2
4	71/M	—	—	NAM	Gastric (advanced)	±0	3/3	3	18,844	Chemo	CS	0.2	Death
5	76/F	Atorvastatin	—	NAM	Gastric (advanced)	±0	4/3	2	5,702	Palliative care	CS, MTX	0.4	Death
6	71/F	—	—	NAM	Lung, thymus (advanced)	±0	3/3	3	8,456	Surgery, Chemo, Rad	CS, MP, IVIg	0.5	Death
7	62/F	Simvastatin	—	NAM	Fallopian tube (advanced)	±0	4/3	4	6,715	Surgery, Chemo	CS, MP, IVIg, MTX	2.7	Death
8	56/F ^c	—	—	NAM	Breast (recurrence) (advanced)	−0.1	2/3	3	6,515	Chemo, Rad	CS	2.5	Death
9	61/F	Simvastatin	—	NAM	Renal pelvis, ureter (advanced)	−0.7	3/3	3	15,970	Rad	CS, IVIg, MTX	0.7	Death
10	60/F	—	—	NAM	Renal pelvis (advanced)	+0.4	4/4	2	16,440	Palliative care	CS, IVCY	0.6	Death
11	67/F	Atorvastatin	—	NAM	Pancreas (advanced)	+0.8	4/5—	1	2,630	Palliative care	CS	1	Death
12	67/F	—	—	NSM	Lung (advanced)	+1.3	3/3	2	8,388	Chemo	CS, MP, IVIg, IVCY, TCR	2.7	Death
13	53/M ^d	—	SRP	NAM	Colon (early)	−12	5—/5—	1	4,846	Surgery	CS, IVIg	2.6	1
14	55/F	—	—	NSM	Colon (early)	−11	3/4	2	4,625	Surgery	CS, IVIg	3.8	0
15	42/M	—	—	NSM	Lymphoma (unclassified)	−7	4/5—	2	23,547	Chemo	CS, MP, IVIg, MTX	0.7	5

Abbreviations: Chemo = chemotherapy; CK = creatine kinase; CS = oral corticosteroid; DM = dermatomyositis; ENMC = European Neuromuscular Centre; IVCY = IV cyclophosphamide; IVIg = IV immunoglobulin; LE = lower extremities; MP = methylprednisolone pulse; MRC = Medical Research Council; mRS = modified Rankin scale; MSA = myositis-specific autoantibodies; MTX = methotrexate; NAM = necrotizing autoimmune myopathy; NSM = nonspecific myositis; PSL = prednisolone; Rad = radiation; SRP = signal recognition particle; TCR = tacrolimus; UE = upper extremities.

^a The follow-up period was defined as the duration between the time of myopathy diagnosis and the last visit.

^b This patient was classified as probable DM with typical skin rash. Cancer stage was unclassified because he developed lymphoepithelial carcinoma as a cervical lymph node metastasis of occult primary cancer.

^c This patient had multiple metastatic recurrences in lymph nodes, despite surgical removal of primary lesion 3.8 years before myopathy diagnosis.

^d This patient showed asymptomatic hyperCKemia (>1,000 IU/L) over 12 years from removal of cancer. He developed mild proximal muscle weakness with further elevation of CK level shortly before pathologic diagnosis.

Table 3 Clinical courses of cancer-free anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody myopathy patients

Patient	Onset age, y/sex	Statin exposure	Other MSA ^a	Classification by ENMC	Pretreatment			Immunosuppressive treatment		At last visit			Sustained elevation of CK level	
					MRC, UE/LE	mRS	CK level, IU/L	Overall	Medications at last visit	MRC, UE/LE	mRS	CK level, IU/L		Follow-up period, y ^a
1	58/F	—	—	NAM	3/3	3	5,152	CS, IVIg, MTX	PSL 10 mg/d, MTX 4 mg/wk	4/5	1	198	3.1	—
2	64/M	—	—	NAM	4/3	2	6,112	CS, MP, IVIg, AZA	PSL 10 mg/d	5/5	2	71	3.4	—
3	30/F	—	—	NSM	4/5	2	7,432	CS, MP	PSL 1 mg/d	5/5	1	157	4	—
4	62/F ^b	—	—	DM	4/4	3	15,870	CS, IVCY, MTX	PSL 6 mg/d	5/4	1	110	5.9	—
5	42/F	—	SRP	NAM	5/3	3	4,532	CS, MP, MTX	MTX 2 mg/wk	5/4	2	126	10.7	—
6	69/F	—	—	NSM	3/4	4	9,269	CS, MTX → AZA	PSL 5 mg/d, AZA 50 mg/d	NI	3	648	3.8	+
7	47/M	—	—	NAM	4/4	3	5,651	CS, MP, MTX	PSL 10 mg/d, MTX 16 mg/wk	3/3	4	297	10.7	+
8	39/F	—	—	Unclassified	4/3	2	7,960	CS, MP, IVIg, AZA	PSL 10 mg/d	5/5	1	4,004	3.7	+
9	43/M	—	—	NAM	5-/5-	1	10,743	CS, MP, IVIg, MTX → TCR	PSL 15 mg/d	5/5	0	2,908	5.1	+
10	31/F ^c	—	—	NAM	4/4	2	10,889	CS, MP, IVIg, TCR → MTX	PSL 20 mg/d, MTX 6 mg/wk	5/5	0	1,701	6.5	+

Abbreviations: AZA = azathioprine; CK = creatine kinase; CS = oral corticosteroid; DM = dermatomyositis; ENMC = European Neuromuscular Centre; IVCY = IV cyclophosphamide; IVig = IV immunoglobulin; LE = lower extremities; MP = methylprednisolone pulse; MSA = myositis-specific autoantibodies; MRC = Medical Research Council; mRS = modified Rankin scale; MTX = methotrexate; NAM = necrotizing autoimmune myopathy; NI = no information; NSM = nonspecific myositis; PSL = prednisolone; SRP = signal recognition particle; TCR = tacrolimus; UE = upper extremities.

^a The follow-up period was defined as the duration between the time of myopathy diagnosis and the last visit.

^b This patient was classified as probable DM with typical skin rash.

^c This patient developed proximal weakness of her upper extremities subacutely with increased CK levels (>10,000 IU/L) at 9 months of pregnancy and received emergent cesarean operation.

was effective for improving muscle strength and decreasing CK level, which led to clinical remission.

DISCUSSION In this study, to determine whether cancer association becomes a risk factor other than statin exposure for anti-HMGCR Ab+ myopathy, we analyzed the clinical courses including the presence of statin exposure and the development of cancer in 33 patients with anti-HMGCR Ab+ myopathy, whom we identified among 621 patients with IIM (33/621, 5.3%).

We found that the prevalence rate of cancer detection within 3 years of myopathy diagnosis (cancer association) among patients with anti-HMGCR Ab+ myopathy was 36% (12/33), which was higher than that of statin exposure (21%) (4 patients had both cancer association and statin exposure). In 12 patients with cancer association, the associated cancers were detected mostly (92%) within 1 year of myopathy diagnosis and frequently (83%) at an advanced stage. In addition, 67% (8/12) of our patients were not exposed to statins. In analysis of cancer risk, the SIR of cancers in patients with anti-HMGCR Ab+ myopathy was extremely high within 1 year of myopathy diagnosis.

In previous large-scale studies, the prevalence rates of cancers in patients with anti-HMGCR Ab+ myopathy ranged from 4% to 26% (irrespective of the temporal association between cancer detection and myopathy diagnosis).^{1,4,5,8–10} In this study, the prevalence rate of cancer association in patients with anti-HMGCR Ab+ myopathy is higher than those in previous reports. However, considering the close temporal association between cancer detection and myopathy diagnosis, extremely increased risk of cancer within 1 year of myopathy diagnosis, and the frequent association of the myopathy with cancer in an advanced stage, there should be some biological link between cancer association and anti-HMGCR Ab+ myopathy development.

Regarding the pathogenesis of anti-HMGCR Ab+ myopathy, it has been suggested that the genetic susceptibility of patients and environmental triggers including statin exposure or unknown factors in statin-naïve patients would be pathogenesis-relevant factors.^{11,12} Taking these into consideration together with the finding that two-thirds of the patients were statin-naïve, cancer is a factor closely associated with anti-HMGCR Ab+ myopathy development in our 12 patients. The difference in the prevalence rate of cancer association between our series and previous reports may be attributable to differences in genetic background and the intensity of cancer screening in patients.

Recently, in the NAM subset of IIMs, it has been reported that the frequency of cancer association is

increased in MSA-negative NAM and anti-HMGCR Ab+ NAM than in anti-SRP Ab+ NAM.¹³ In comparison with the previous study, our study is different in that we showed cancer association in anti-HMGCR Ab+ myopathy, not limited to NAM subsets of IIMs. Indeed, in our 12 patients with cancer association, 4 patients with non-NAM subsets of IIMs were included (NSM, n = 3; DM, n = 1). Our study shows the association between cancer and anti-HMGCR Ab+ myopathy regardless of pathologic subtypes. Considering the close synchronous occurrence of cancers and myopathies in our 12 patients (the detection of cancer was confined within 1.3 years of myopathy diagnosis), along with the finding that there were no patients with cancers detected after 3 years of myopathy diagnosis, cancer association is at least one of the factors that triggered anti-HMGCR Ab+ myopathy.

Notably, one man with cancer history, who was dual positive for anti-HMGCR Ab and anti-SRP Ab as reported elsewhere,^{10,18,19} showed a sustained increase in CK level over 12 years from cancer removal to the development of symptomatic myopathy shortly before pathologic diagnosis (figure 1). The clinical course of this patient is similar to that of statin-exposed patients who tolerated statin exposure for a long duration before the development of symptomatic myopathy.¹¹ In our patient, it would be likely that the autoimmune processes initially started, triggered by cancer, and he tolerated it for 12 years until some additional unknown factors induced the development of symptomatic myopathy.

The low prevalence rate of statin-exposed patients in anti-HMGCR Ab+ myopathy in Asian countries is already reported.^{7,8,10} In our series, all 10 cancer-free patients were statin-naïve, which suggested that there were unknown risk factors for developing anti-HMGCR Ab+ myopathy other than cancer association or statin exposure. In addition, interestingly, 3 cancer-free patients showed full or almost full recovery of muscle strength despite markedly elevated CK levels. Similar clinical courses have been reported in both statin-exposed and statin-naïve patients.^{1,3,20,21} A sustained increase in CK levels with mild weakness in these patients including our 3 patients supports the suggestion that development of symptomatic myopathy requires additional unknown factors including environmental triggers,²¹ which remain to be elucidated.

Mechanisms underlying anti-HMGCR Ab+ myopathy remain unknown, and only statin, genetic susceptibility, environmental triggers, or both have been suggested.¹² In this study, we found cancer association was more frequent than statin exposure in our cohort, and most of the associated cancers were in an advanced stage and were detected within 1 year of myopathy diagnosis. Our findings suggest that cancer association is one of the risk factors for the development of anti-HMGCR Ab+ myopathy.

AUTHOR CONTRIBUTIONS

Dr. Kadoya contributed to evaluation of the patients, acquisition of data, analysis and interpretation, and preparation of the manuscript. Dr. Kaida contributed to analysis and interpretation, study supervision, and revision of the manuscript. Dr. Shimizu contributed to study concept and design, data acquisition, analysis and interpretation, and critical revision of the manuscript for important intellectual content. Drs. Taira, Ikenaga, Uchio, Hida, Kubota, Miwa, Kurasawa, Shimada, Sonoo, Chiba, Shio, Uesaka, Sakurai, and Izumi contributed to acquisition of data. Dr. Maeda contributed to study supervision and revision of the manuscript. Dr. Inoue contributed to analysis and interpretation. Drs. Kwak and Tsuji contributed to study concept and designs, study supervision, and revision of the manuscript.

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