CLINICAL STUDY

The Risk of Ventricular Tachyarrhythmias in Patients with Antimitochondrial Antibodies-Related Noncardiac Diseases

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Summary

Antimitochondrial antibodies (AMA) are serum autoantibodies specific to primary biliary cholangitis and are linked to myopathy and myocardial damage; however, the presence of AMA as a risk factor for ventricular tachyarrhythmias (VTs) has remained unknown. This study aimed to elucidate whether the presence of AMA-related noncardiac diseases indicates VTs risk.

This cohort study enrolled 1,613 patients (883 females) who underwent AMA testing to assess noncardiac diseases. The incidence of VTs and supraventricular tachyarrhythmias (SVTs) from a year before the AMA testing to the last visit of the follow-up were retrospectively investigated as primary and secondary objectives. Using propensity score matching, we extracted AMA-negative patients whose covariates were matched to those of 152 AMA-positive patients. In this propensity score-matched cohort, the incidence of VTs and SVTs in the AMA-positive patients were compared with that in AMA-negative patients.

The AMA-positive patients had higher estimated cumulative incidence (log-rank, $P = 0.013$) and prevalence (5.9% versus 0.7%, $P = 0.020$) of VTs than the AMA-negative patients. The presence of AMA was an independent risk factor for VTs (hazard ratio, 4.02; 95% CI, 1.44-20.01; $P = 0.005$). Meanwhile, AMA were associated with atrial flutter and atrial tachycardia development. In AMA-positive patients, VTs were associated with male sex, underlying myopathy, high creatine kinase levels, presence of chronic heart failure or ischemic heart disease, left ventricular dysfunction, presence of SVTs, and the electrocardiographic parameters indicating atrial disorders.

The presence of AMA-related noncardiac diseases is an independent risk factor for VTs.

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Key words: Arrythmia, Electrocardiogram, Primary biliary cholangitis, Myopathy

Antimitochondrial antibodies (AMA) are serum autoantibodies specific to primary biliary cholangitis (PBC).[1-5] AMA recognize mitochondrial antigens and have been associated with some types of myositis.[1-5] Compared with other myositis types, AMA-associated myositis is characterized by a chronic progression of skeletal muscle atrophy and weakness of the respiratory muscles.[1,4] AMA are now considered important not only as a marker for inflammatory myopathy subgroups but also as a factor involved in the underlying mechanisms of myositis pathogenesis.[5] Furthermore, AMA-positive patients have been reportedly prone to myocardial damage and arrhythmias.[1,2,6-11] Presently, although supraventricular arrhythmia may be the most common cardiac complication associated with AMA,[1,6] severe ventricular arrhythmia has also been reported in some cases.[2] The development of these ventricular tachyarrhythmias (VTs) is an important concern as a life-threatening risk.[12] However, the presence of AMA as a risk factor for arrhythmic diseases, particularly ventricular arrhythmias, remains unproven, and its clinical features are still poorly understood. Additionally, there is a potential risk of missing the risk of AMA-related cardiomyopathy or arrhythmias because AMA test is mainly performed in other departments, not in the cardiovascular one. Thus, this study aimed to clarify whether the presence of AMA-related noncardiac diseases is a risk factor for ventricular tachyarrhythmias.

Methods

Study population: We retrospectively analyzed data from a series of patients who were assessed for the presence of AMA in a noncardiac department of our hospital between

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June 2012 and May 2020. We included patients who were assessed for liver injury, myopathy, or collagen disease via AMA testing with the following conditions: (1) hepatic injury, indicated by abnormalities such as elevated hepatobiliary enzyme levels (> 1.5 times the normal limit), (2) muscle disorders, indicated by such signs as drooping head or difficulty walking, or (3) collagen diseases suspected from symptoms such as fever and Raynaud's phenomenon. Because of the retrospective design of the study, we did not obtain written informed consent; instead, we used an opt-out method of informed consent, which was based on a statement displayed on our hospital's website, according to Japanese clinical research guidelines. This study followed the ethical guidelines outlined in the Declaration of Helsinki. The Research Ethics Review Committee for Research Involving Human Participants of Niigata University also approved the study protocol (No. 2019-0442).

Hypertension was defined by a systolic blood pressure ≥ 140 mmHg or the intake of oral antihypertensive drugs. Diabetes was defined by a fasting blood glucose ≥ 126 mg/dL, casual blood glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, or the intake of oral hypoglycemic agents. Patients with chronic heart failure were defined as those who had left ventricular ejection fraction (LVEF) < 40% or who satisfied the previously published Framingham criteria.[13] Furthermore, ischemic heart diseases were defined as a treatment history of those or the presence of significant coronary artery stenosis ≥ 75%. We used the medical records at the last visit to determine the final diagnosis of the initial disorders that required AMA testing. We excluded those patients who had not been measured for creatine kinase (CK) or had not undergone 12-lead electrocardiography (ECG) since the day a year before the AMA testing. Figure 1 illustrates a flowchart of the inclusion and exclusion criteria.

Definition of arrhythmias and measurement of ECG parameters: During the follow-up period, that is from a year before the AMA testing to the last visit to our hospital, arrhythmias were detected based on 12-lead ECG, 24-hour Holter ECG recordings. Holter ECG recordings were performed mainly when the patient complained of palpitation or when ECG abnormalities or structural heart diseases were observed. Atrial fibrillation (AF), atrial flutter (AFL), atrial tachycardia (AT), and paroxysmal supraventricular tachycardia (PSVT) lasting ≥ 30 seconds and/or lasting during a 12-lead electrocardiogram indicated supraventricular tachyarrhythmias (SVTs). AF was defined as irregular R-R intervals with typical fibrillation at baseline testing. AFL was defined as the presence of characteristic regular flutter waves without an isoelectric baseline between the atrial deflections in at least a single lead. AT was defined as regular narrow QRS tachycardia with ectopic P-waves. PSVT was defined as regular narrow QRS tachycardia with retrograde P-waves or without P-waves. Ventricular tachycardia at a rate equal to or higher than 100 beats per minute and ventricular fibrillation lasting ≥ 30 seconds, along with ≥ 5 consecutive nonsustained ventricular tachycardia (NSVT), were defined as VTs.

The ECG parameters, which were obtained closest to the time of AMA measurement, were analyzed. The heart rate, PR interval, QT interval, QTc interval, QRS duration, QRS axis, P-wave amplitude in lead II, P-wave duration, and P-wave axis were measured. The P-wave axis was calculated from the P-wave amplitude in leads I and III.

Laboratory analysis: AMA were evaluated using the AMA measured by indirect immunofluorescence (IIF-AMA) test (SRL, Inc., Tokyo, Japan) or the AMA-M2 test measured by chemiluminescent enzyme immunoassay (LSI Medience Corp., Tokyo, Japan). A patient was considered positive for AMA if the IIF-AMA accumulated over 20-fold and/or the AMA-M2 was > 7.0 U/mL. Blood tests, which were also performed closest to the time of the AMA measurement, were analyzed. We evaluated the levels of blood urea nitrogen, creatinine, aspartame transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, CK, total blood protein, and albumin.

Transthoracic echocardiography: Transthoracic echocardiography was performed mainly when ECG abnormalities were observed, there was a history of heart failure, or heart failure symptoms similar to Framingham criteria are observed; we analyzed those performed closest to the time of the AMA measurement. The left atrial diameter (LAD), the left ventricular end-diastolic/end-systolic diameter (LVDd/LVDs), the left ventricular posterior wall, and interventricular septum thickness were measured using the parasternal long-axis images. Additionally, LVEF was measured via the Teichholz method or the modified Simpson method. If both were measured in a patient, the latter was preferred.

Endomyocardial biopsy: Endomyocardial biopsy was evaluated in some patients with VTs via optical and electron microscope examinations to determine any presence of myocyte degradation, inflammatory cell infiltration, fibrosis, and mitochondrial degeneration.

Statistical methods: AMA-negative patients (controls) that matched with AMA-positive patients were extracted by propensity score matching to balance the covariates between such patient groups. Propensity scores for each patient were calculated; the independent variables were age, sex, the presence of chronic heart failure, ischemic heart disease, a history of prior open-heart surgery, and the underlying disease classification (liver injury, myopathy, or collagen disease). The logit-transformed propensity score was matched with the closest case using calipers of 0.019 in a 1:1 manner. The patient background, blood test findings, ECG parameters, and echocardiography parameters were compared between the two groups. The normally distributed data were compared using Student's t test, whereas the nonnormally distributed data were compared using the Mann-Whitney U test. Meanwhile, the categorical variables were compared using Pearson's chi-square test or Fisher's exact test.

As the primary objective, via the Kaplan-Meier method, we compared the cumulative incidence of VTs from a year before AMA testing between the AMA-positive and AMA-negative groups. As a secondary objective, the cumulative incidence of SVTs between two groups was also analyzed. Furthermore, the risk factors

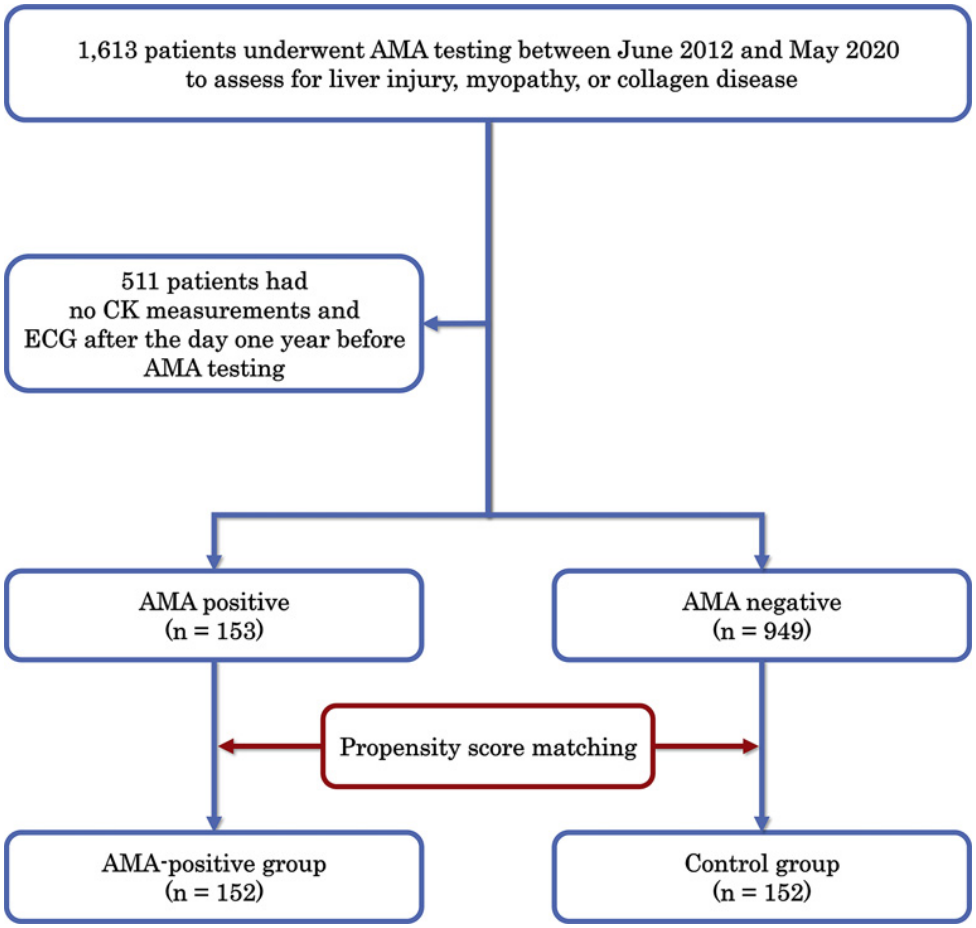

Figure 1. Flowchart of participant selection. Propensity scores for each patient were calculated using age, sex, presence of chronic heart failure, ischemic heart disease, prior history of open-heart surgery, and the underlying disease classification (liver injury, myopathy, or collagen disease) as independent variables. Propensity score matching was used for establishing antimitochondrial antibodies (AMA) positive and AMA-negative (control) groups. The cohort was created in a 1:1 ratio. CK indicates creatine kinase; and ECG, electrocardiography.

for VTs events were analyzed via a Cox proportional hazards model. Patients without VTs were discontinued on the last follow-up date. Only variables with $P < 0.1$ from the univariate analysis were incorporated into the multivariate analysis. The final multivariate model was constructed via backward elimination.

Continuous variables are expressed as mean and standard deviation in normally distributed data, but as median and first quartile-third quartile in nonnormally distributed data. Meanwhile, categorical variables are expressed as numerical values (%). Additionally, $P < 0.05$ was considered significant. All statistical data were analyzed via JMP Pro 16.0 (SAS Institute, Cary, North Carolina, USA).

Results

During the 9-year inclusion period, we enrolled 1,613 patients who underwent IIF-AMA/AMA-M2 testing to assess for liver injury, myopathy, or collagen disease. Of those, 1,536 patients (95%) underwent the AMA-M2 testing, whereas 751 patients underwent the IIF-AMA testing. However, 511 patients were excluded because of missing CK measurements or ECG 1 year before the AMA testing. Finally, this study included 153 AMA-positive patients and 949 AMA-negative patients. A 1:1 matching cohort of AMA-positive and negative patients was created through propensity score matching. Ultimately, we matched 152 AMA-positive patients and 152 AMA-negative patients and regarded them as the AMA-positive and control groups, respectively (Figure 1).

Differences between the AMA-positive and control groups: Table I lists the clinical characteristics of both groups. The mean follow-up period tended to be longer in the AMA-positive group (1,498 ± 1,071 days) compared with the control group (1,292 ± 917 days) but was not significantly different between the two groups (P = 0.072). Age, sex, and AMA testing objectives showed no significant differences. PBC was more prevalent in the AMA-positive group at the final diagnosis of AMA-related disorders than in the control group, but no significant difference was found in myopathies.

AMA-positive determination was assessed using the

Table I. Baseline Demographic Characteristics of the Participants

	Control group (n = 152)	AMA-positive group (n = 152)	P value
Age, years	66 (57–73)	65 (56–73)	0.78
Female	116 (76.3%)	113 (74.3%)	0.69
Purpose of the AMA test			
Hepatic dysfunctions	125 (82.2%)	116 (76.3%)	0.20
Myopathies	25 (16.5%)	32 (21.1%)	0.30
Collagen diseases	2 (1.3%)	4 (2.6%)	0.68
Final diagnosis of disorders requiring AMA test			
Primary biliary cholangitis	1 (0.7%)	94 (61.8%)	< 0.001
Autoimmune hepatitis	11 (7.2%)	18 (11.8%)	0.17
Other liver diseases	112 (73.7%)	28 (18.4%)	< 0.001
Myopathies	22 (14.5%)	31 (20.4%)	0.17
Collagen diseases	4 (2.6%)	8 (5.3%)	0.38
Others	4 (2.6%)	2 (1.3%)	0.68
Comorbidities			
Hypertension	63 (41.5%)	56 (36.8%)	0.41
Diabetes	36 (23.7%)	25 (16.5%)	0.11
Chronic heart failure	7 (4.6%)	8 (5.3%)	0.79
Ischemic heart disease	8 (5.3%)	6 (4.0%)	0.58
Open heart surgery	3 (2.0%)	3 (2.0%)	1
Treatment			
β blockers	7 (4.6%)	14 (9.2%)	0.11
ARB/ACE inhibitors	40 (26.3%)	37 (24.3%)	0.69
Calcium channel blockers	40 (26.3%)	38 (25.0%)	0.79
Diuretics (excluding mineralocorticoid receptor antagonists)	17 (11.2%)	22 (14.5%)	0.39
Mineralocorticoid receptor antagonists	12 (7.9%)	8 (5.3%)	0.35
Digitalis	2 (1.3%)	1 (0.7%)	1
Antiarrhythmic agent	4 (2.6%)	3 (2.0%)	0.72
Cardiac devices	2 (1.3%)	4 (2.6%)	0.68
Pacemaker	2 (1.3%)	1 (0.7%)	1
Implantable cardioverter defibrillator	0	3 (2.0%)	0.25

Nonparametric continuous variables are expressed as median (lower quartile–upper quartile). AMA indicates antimitochondrial antibody; ARB, angiotensin II receptor blocker; and ACE, angiotensin-converting enzyme.

AMA-M2 test measured by chemiluminescent enzyme immunoassay rather than indirect immunofluorescence assay in most cases. Naturally, the AMA-M2 titer was higher in the AMA-positive group than in the control group (Table II). According to the baseline blood test results, the AMA-positive group had lower AST and ALT levels and higher CK levels than the control group. The AMA-positive group also had a significantly lower heart rate than the control group (Table II). Meanwhile, 58 (38%) control patients and 75 (49%) AMA-positive patients underwent transthoracic echocardiography, and the echocardiographic parameters were not significantly different between such groups (Table II).

Figure 2 illustrates the prevalence of tachyarrhythmias in both groups. The AMA-positive group also had a significantly higher prevalence of VTs, which were found in 9 patients (6%). No patients in either group developed ventricular fibrillation. Regarding the primary objective, the AMA-positive group had a higher estimated cumulative incidence of VTs than the control group (log-rank, P = 0.013) (Figure 3). In the AMA-positive group, AMA-M2 titer did not correlate with any of the coexisting conditions, such as chronic heart failure, VTs development, heart rate, and CK levels. Of the 9 AMA-positive patients with VTs, 4 had episodes of sustained ventricular tachycardia. The remaining 5 AMA-positive patients had NSVT with 7-28 consecutive beats. Two patients with sustained ventricular tachycardia underwent catheter ablation for reentrant ventricular tachycardia of left ventricular origin. An AMA-negative patient with VTs had an episode of 12 consecutive beats of NSVT; this patient was observed without any treatment because the left ventricular function was preserved (LVEF = 70.1%). The final multivariate model constructed via backward elimination showed that AMA positivity, the presence of myopathies, the presence of ischemic heart diseases, and history of SVTs were independently associated with an increased risk for VTs development, with a hazard ratio of 4.02 (95% CI, 1.44-20.01; P = 0.005) for the presence of AMA (Table III). VTs were more prevalent among the AMA-positive patients (5.9%) than among the controls (0.7%; P = 0.020).

Regarding the secondary objective, SVTs were found in 16 controls (AF in 13, AT/AFL in 2, and PSVT in 1) and in 22 AMA-positive patients (AF in 8, AT/AFL in 13, and PSVT in 1) (Figure 2). Although the prevalence of SVTs did not differ between the two groups, AT or AFL was more common among the AMA-positive patients (8.6%) than among the controls (1.3%; P = 0.006).

Risk factors of VTs development in the AMA-positive group: To identify the risk factors of VTs in AMA-

Table II. Baseline Laboratory Parameters and Physiological Tests

	Control group (n = 152)	AMA-positive group (n = 152)	P value
Laboratory parameters			
Blood urea nitrogen, mg/dL	14 (10–19)	14 (11–19)	0.75
Creatinine, mg/dL	0.61 (0.50–0.83)	0.61 (0.50–0.73)	0.43
Aspartate aminotransferase, IU/L	52 (28–108)	39 (28–77)	0.046
Alanine aminotransferase, IU/L	55 (27–154)	36 (21–67)	0.007
Lactate dehydrogenase, IU/L	230 (187–286)	224 (183–274)	0.33
Alkaline phosphatase, IU/L	302 (215–423)	346 (213–545)	0.11
Gamma-glutamyl transferase, IU/L	100 (33–225)	99 (30–219)	0.76
Total bilirubin, mg/dL	0.7 (0.5–1.1)	0.7 (0.6–1.0)	0.82
Creatine kinase, IU/L	57 (34–103)	86 (52–137)	0.001
AMA-M2, U/mL*	1.3 ± 1.0	101.1 ± 101.8	< 0.001
Electrocardiographic findings			
Heart rate, beats/minute	75 (66–85)	72 (64–79)	0.014
PR interval, millisecond	158 (145–174)	157 (142–172)	0.73
QT interval, millisecond	386 (364–409)	391 (373–420)	0.011
QTc interval, millisecond	427 (413–448)	428 (412–444)	0.88
QRS duration, millisecond	94 (89–101)	93 (89–101)	0.83
QRS axis, degree	39 (14–61)	45 (17–66)	0.62
P-wave amplitude, mV	0.11 (0.07–0.14)	0.10 (0.07–0.13)	0.27
P-wave duration, millisecond	104 (92–108)	100 (92–116)	0.59
P-wave axis, degree	58 (41–69)	60 (46–71)	0.48
Echocardiographic findings†			
Ejection fraction, %	69.4 (63.9–72.8)	69.0 (63.0–73.8)	0.74
Left atrial dimension, mm	35.0 (31.8–40.9)	34.0 (30.1–39.1)	0.51
Left ventricular end-diastolic dimension, mm	43.0 (39.8–45.9)	42.5 (38.6–48.0)	0.94
Left ventricular end-systolic dimension, mm	26.5 (24.0–29.7)	25.0 (22.4–30.0)	0.20
Interventricular septal thickness, mm	9.0 (8.0–10.0)	9.0 (8.0–10.7)	0.48
Left ventricular posterior wall thickness, mm	9.1 ± 1.5	9.1 ± 1.5	0.83

Nonparametric continuous variables are expressed as median (lower quartile–upper quartile). AMA indicates antimitochondrial antibody. *Control group (n = 147), AMA-positive group (n = 49). †Control group (n = 58), AMA-positive group (n = 75).

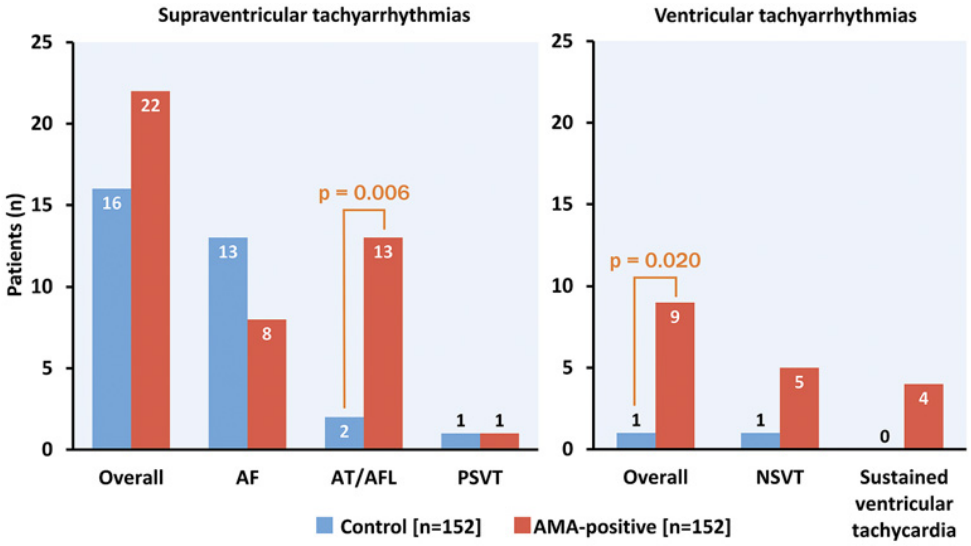

Figure 2. Tachyarrhythmias in the control and the antimitochondrial antibodies (AMA) positive groups. Atrial tachycardia (AT) or atrial flutter (AFL) was prevalent in the AMA-positive group by 7.2%, which was more frequent than in the control group (P = 0.006). The frequency of ventricular tachyarrhythmias, including nonsustained ventricular tachycardia (NSVT) and sustained ventricular tachycardia, was higher in the AMA-positive group than in the control group (P = 0.020). AF indicates atrial fibrillation; and PSVT, paroxysmal supraventricular tachycardia.

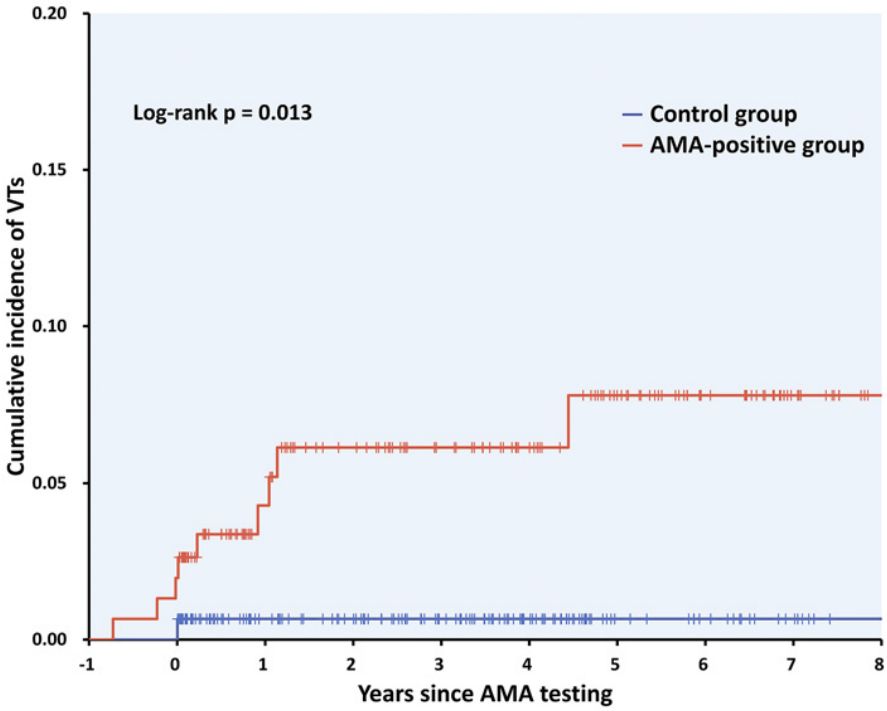

Figure 3. Cumulative incidence of ventricular tachyarrhythmias (VTs). It was calculated starting from a year before antimitochondrial antibodies (AMA) testing. The estimated cumulative incidence of VTs was higher in the AMA-positive group than in the control group (log-rank, $P = 0.013$).

Table III. Univariate and Multivariate Cox Proportional Hazards Models with Backward Elimination for Predicting Ventricular Tachyarrhythmia Development

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age, years	0.983	0.94–1.03	0.43			
Female	0.442	0.22–0.83	0.012	0.575	0.28–1.10	0.096
AMA	2.969	1.29–12.75	0.007	4.015	1.44–20.01	0.005
Heart rate, beats/minute	1.018	0.98–1.06	0.40			
QRS duration, millisecond	1.033	1.01–1.05	0.019			
QRS axis, degree	0.982	0.97–1.00	0.018			
QTc interval, millisecond	1.022	1.00–1.04	0.016			
Creatine kinase, per decade IU/L	1.003	0.99–1.01	0.40			
Myopathies	3.312	1.75–7.14	< 0.001	2.949	1.23–8.49	0.015
Hypertension	1.287	0.68–2.44	0.43			
Diabetes	1.099	0.43–2.20	0.82			
Chronic heart failure	3.022	1.40–5.74	0.008			
Ischemic heart disease	2.592	1.00–5.23	0.050	4.920	1.60–15.12	0.008
Supraventricular tachyarrhythmia	3.835	2.02–7.28	< 0.001	2.167	1.03–4.88	0.042

Variables with $P < 0.1$ in the univariate analysis (female, AMA, QRS duration, QRS axis, QTc interval, myopathies, chronic heart failure, ischemic heart disease, and supraventricular tachyarrhythmia) were used in the multivariate analysis. AMA indicates antimitochondrial antibodies; and CI, confidence interval.

positive patients, we further divided this group into patients with and without VTs (VTs group [$n = 9$] and VTs-free group [$n = 143$], respectively). Table IV presents the clinical features of both groups. Regarding the type of final diagnosis of the disorders that required AMA testing, the VTs group had a significantly lower prevalence of liver injury and a higher prevalence of myopathies. Male sex, presence of chronic heart failure, presence of ischemic heart diseases, history of SVTs, β-blockers use, calcium channel blockers use, and diuretics use were significantly more prevalent in the VTs group than in the VTs-free group. In terms of blood tests, CK levels were significantly higher in the VTs group than in the VTs-free group (Table V). The electrocardiographic parameters indicated that the P-wave amplitude was significantly lower in the VTs group than in the VTs-free group. Compared

Table IV. Comparison of Baseline Demographic Characteristics between AMA-Positive Patients with and without VTs

	VTs-free group (n = 143)	VTs group (n = 9)	P value
Age, years	66 (56–73)	62 (54–66)	0.30
Female	110 (76.9%)	3 (33.3%)	< 0.001
Purpose of the AMA test			
Hepatic dysfunctions	114 (79.7%)	2 (22.2%)	< 0.001
Myopathies	25 (17.5%)	7 (77.8%)	< 0.001
Collagen diseases	4 (2.8%)	0	1
Final diagnosis of disorders requiring AMA test			
Primary biliary cholangitis	90 (62.9%)	4 (44.4%)	0.30
Autoimmune hepatitis	18 (12.6%)	0	0.60
Other liver diseases	28 (19.6%)	0	0.21
Myopathies	24 (16.8%)	7 (77.8%)	< 0.001
Collagen diseases	8 (5.6%)	0	1
Other	2 (1.4%)	0	1
Comorbidities			
Hypertension	52 (36.4%)	4 (44.4%)	0.73
Diabetes	23 (16.1%)	2 (22.2%)	0.64
Chronic heart failure	5 (3.5%)	3 (33.3%)	0.007
Ischemic heart disease	4 (2.8%)	2 (22.2%)	0.042
Open heart surgery	3 (2.1%)	0	1
Supraventricular tachyarrhythmias	6 (4.2%)	5 (55.6%)	< 0.001
Treatment			
β blockers	7 (4.9%)	7 (77.8%)	< 0.001
ARB/ACE inhibitors	33 (23.1%)	4 (44.4%)	0.22
Calcium channel blockers	33 (23.1%)	5 (55.6%)	0.044
Diuretics (excluding mineralocorticoid receptor antagonists)	18 (12.6%)	4 (44.4%)	0.026
Mineralocorticoid receptor antagonists	7 (4.9%)	1 (11.1%)	0.39
Digitalis	1 (0.7%)	0	1
Antiarrhythmic agent	1 (0.7%)	2 (22.2%)	0.009

Nonparametric continuous variables are expressed as median (lower quartile–upper quartile). VTs indicates ventricular tachyarrhythmias; AMA, antimitochondrial antibodies; ARB, angiotensin II receptor blocker; and ACE, angiotensin-converting enzyme.

with that in the VTs-free group, the P-wave axis in the VTs group significantly deviated to the left axis (Table V). Lastly, echocardiography revealed significantly lower LVEF, larger LAD, and larger LVDd/LVDs in the VTs group than in the VTs-free group (Table V).

Endomyocardial biopsy findings: We sampled the right ventricular septum of two patients with sustained ventricular tachycardia for the endomyocardial biopsy. One had no apparent cause of myocardial dysfunction other than AMA-related cardiomyopathy, whereas the other was a case of diffuse left ventricular dysfunction with a history of old inferior wall myocardial infarction. In the former myocardial biopsy, the mitochondria in the cardiomyocytes were severely degenerated, as shown in electron microscopy (Figure 4). Meanwhile, mitochondrial swelling and vacuolated mitochondria were found in the latter.

Discussion

To our knowledge, this study had the largest cohort of AMA-positive patients for long-term, detailed investigation of ventricular arrhythmias. The main finding of this study was that the AMA-positive group had a higher estimated cumulative incidence of VTs than the control group. The presence of AMA was an independent risk factor for VTs in the patients who have assessed AMA for a noncardiac cause with matching propensity scores (Table III). Interestingly, the AMA-positive patients with VTs were mostly males compared with those without VTs. In the AMA-positive group, VTs development is associated with myopathy (as an underlying disease), high CK levels, low LVEF, left atrial enlargement, low P-wave amplitude, leftward deviation of the P-wave axis, and coexistence of either chronic heart failure, ischemic heart disease or SVTs (Table IV and V).

Differences between the AMA-positive and control groups: This study showed that the presence of AMA is an independent risk factor of VTs among the patients who were tested for AMA in the noncardiovascular department. Recently, supraventricular arrhythmias had been reportedly associated with the presence of AMA.[1,6] Additionally, the presence or absence of myopathies may not necessarily be associated with the onset of arrhythmia according to the report.[6] These results are similar to the association between VTs and AMA found in this study.

This study also found that heart rate was lower in the AMA-positive group than in the control group. Keresztes, *et al.* reported that AMA-positive patients with PBC had a higher frequency of autonomic dysfunction and a lower heart rate response to deep breathing, standing, and Valsalva maneuver.[14] According to the cases with AMA-associated myocardial damage, disorders of the conduction system were observed.[1,10] Thus, the decreased heart rate in AMA-positive patients observed in this study may

Table V. Comparison of Baseline Laboratory Parameters and Physiological Test Results between AMA-Positive Patients with and without VTs

	VTs-free group (n = 143)	VTs group (n = 9)	P value
Laboratory parameters			
Blood urea nitrogen, mg/dL	14 (11–19)	13 (11–21)	0.90
Creatinine, mg/dL	0.61 (0.50–0.74)	0.61 (0.43–0.67)	0.38
Aspartate aminotransferase, IU/L	39 (28–67)	50 (30–67)	0.63
Alanine aminotransferase, IU/L	35 (21–72)	40 (23–51)	0.99
Lactate dehydrogenase, IU/L	222 (181–273)	259 (220–304)	0.084
Alkaline phosphatase, IU/L	344 (213–539)	356 (188–659)	0.84
Gamma-glutamyl transferase, IU/L	101 (30–222)	68 (33–232)	0.88
Total bilirubin, mg/dL	0.7 (0.6–1.0)	0.8 (0.6–1.3)	0.84
Creatine kinase, IU/L	82 (50–117)	238 (210–716)	< 0.001
Electrocardiographic findings			
Heart rate, beats/minute	71 (63–79)	76 (69–80)	0.38
PR interval, millisecond	156 (142–170)	182 (132–251)	0.12
QT interval, millisecond	390 (373–420)	399 (372–451)	0.53
QTc interval, millisecond	428 (412–444)	430 (415–489)	0.25
QRS duration, millisecond	93 (89–100)	108 (98–132)	0.090
QRS axis, degree	45 (19–66)	−25 (−43–68)	0.11
P-wave amplitude, mV	0.11 (0.08–0.13)	0.04 (0.03–0.07)	< 0.001
P-wave duration, millisecond	100 (92–112)	108 (98–132)	0.063
P-wave axis, degree	60 (49–71)	−30 (−45–51)	< 0.001
Echocardiographic findings*			
Ejection fraction, %	69.2 ± 8.0	54.1 ± 16.4	0.026
Left atrial dimension, mm	34.0 (30.0–37.1)	39.0 (33.2–45.5)	0.038
Left ventricular end-diastolic dimension, mm	42.7 ± 5.6	49.0 ± 8.0	0.047
Left ventricular end-systolic dimension, mm	24.9 (22.1–29.1)	37.5 (25.6–40.9)	0.002
Interventricular septal thickness, mm	9.0 (8.0–10.3)	9.8 (9.0–12.0)	0.055
Left ventricular posterior wall thickness, mm	9.0 (8.0–10.0)	9.8 (8.4–11.0)	0.31

Nonparametric continuous variables are expressed as median (lower quartile–upper quartile); parametric continuous variables are expressed as mean ± standard deviation. VTs indicates ventricular tachyarrhythmias; and AMA, antimitochondrial antibody. *VTs-free group (n = 66), VTs group (n = 9).

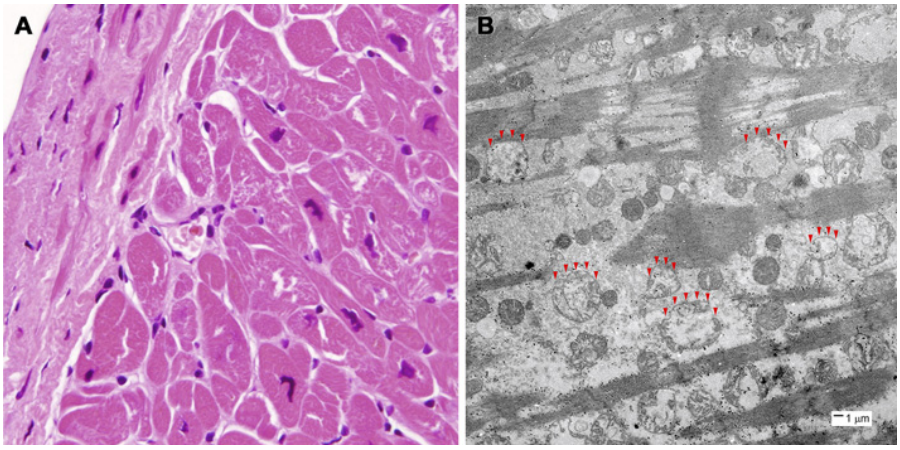

Figure 4. Light (**A**) and electron (**B**) micrographs of a myocardial biopsy. It was a right ventricular septal myocardium collected from a 47-year-old male with sustained ventricular tachycardia and myopathy. **A:** Hematoxylin-eosin staining, 60 times. No accumulation of inflammatory cells or fibrosis was observed in the myocardium. **B:** The mitochondria of cardiomyocytes exhibited severe degeneration (arrowhead indicates the degenerated mitochondria).

be associated with autonomic nervous system and/or cardiac conduction system disorders.

Risk factors of VTs development in the AMA-positive group: Notably, patients with VTs in the AMA-positive group were predominantly male compared with those without VTs (67% versus 23%). While PBC is generally predominant in females,[15,16] this finding is similar to previous reports showing that males with PBC have more heart complications than females.[11] Male sex is also an important risk factor for developing dilated cardiomyopa-

thy and associated cardiac adverse events, but the exact cause remains unknown.[17,18] Thus, the cause of sex difference in AMA-related myocardial damage and VTs is still unclear, thereby requiring further research. In this study, cardiac function or electrocardiographic parameters did not differ between the overall AMA-positive group and the control group. However, high CK levels, P-wave abnormalities, low LVEF, and enlarged left atrial dimension were more common in patients with VTs than in those without VTs in the AMA-positive group. Therefore, AMA might induce the arrhythmic substrate not in all AMA-positive patients, but rather in limited AMA-positive patients.

Histological considerations and a possible mechanism of AMA-associated arrhythmia: The insight into whether AMA act directly on the myocardium is still undetermined. However, concerning the mechanism of AMA-related myocardial damage, case reports suggested that myocardial pathological findings included T cell infiltration and mitochondrial degeneration.[7,19] Meanwhile, the adenine nucleotide translocator, which is abundant in the inner mitochondrial membrane, may become an organ-specific self-antigen inducing mitochondrial damage in dilated cardiomyopathy cases.[20] Further studies are required, given that similar immunological responses might be the causes of AMA-associated myocardial damage.

AMA are an autoantibody against several mitochondrial antigens detected in the sera of patients with PBC via immunoblotting and enzymatic immunoassays.[21] It targets the family of 2-oxo-acid dehydrogenase complexes, which include the E2 subunits of the pyruvate dehydrogenase complex, the sintered-chain 2-oxo-acid dehydrogenase complex, and the ketoglutaric acid dehydrogenase complex, along with the dihydrolipoamide dehydrogenase-binding protein.[15,16] According to the electron microscopic findings from the muscle biopsies of AMA-positive patients, abnormal mitochondrial accumulation was observed in the subsarcolemmal region.[22,23] Although the myocardial pathological findings of AMA-positive cases are still insufficiently understood, Matsumoto, *et al.* reported that the ventricular myocardium of patients with AMA-related cardiomyopathy exhibited interstitial fibrosis with infiltration of CD3-positive T cells.[7] Saito, *et al.* revealed that in the immunohistochemistry of pyruvate dehydrogenase complex-E2 subunit, which is an antigen for AMA-M2 antibodies, the cytoplasm of myocytes and cardiomyocytes in patients with AMA-related myocarditis showed granular staining.[19] In the current study, the mitochondria in the cardiomyocytes of patients with AMA-associated VTs were severely degenerated (Figure 4). Hence, AMA may be directly associated with myocardial mitochondrial damage.

In this study, of 152 AMA-positive patients, 9 (5.9%) had VTs, whereas 13 (8.6%) had AFL or AT. Most of these tachyarrhythmias were characterized by reentrant mechanisms, according to the findings of the electrophysiologic study. It has been reported that local mitochondrial depolarization caused by myocardial mitochondrial disorders may shorten the action potentials and the refractory period by amplifying the sarcolemmal ATP-sensitive K(+) currents, which consequently promotes reentrant arrhythmias.[24] These electrophysiological changes caused by mitochondrial disorders may be partly responsible for the development of tachyarrhythmias in AMA-positive patients. The prevalence of VTs was higher in this study than in previous reports,[1,6] possibly because the follow-up period (1,395 ± 1,001 days) after AMA testing was longer than in other studies. Low P-wave amplitude and deviation of the P-wave axis, which suggest a conduction injury in the atrium, were often observed on the electrocardiograms of AMA-positive patients with VTs in this study (Table II). Additionally, many AMA-positive patients who develop VTs have a history of SVTs at the time of AMA testing (Table IV), and in AMA-positive patients, a history of SVTs is also an independent risk factor for developing VTs (Table III). Therefore, ventricular myocardium injuries and VTs may become evident after atrial myocardium injuries.

Limitations: Our study has some potential limitations. First, this retrospective cohort study focused on investigating relationships; thus, a causal association could not be established. Nevertheless, the propensity score matching aided in the establishment of a control population similar to the AMA-positive group by excluding 84% of AMA-negative patients. Second, given that this study was conducted in a single center, it may not represent the general population of AMA-positive patients in noncardiac department. Third, the information in medical records was not always complete; hence, comorbidity may be underestimated. Moreover, the prevalence of arrhythmia might be underestimated because the arrhythmia was asymptomatic or could not be captured on the electrocardiogram. Fourth, 511 patients who underwent AMA testing mainly for liver injury were excluded because CK measurement or electrocardiogram was not performed. Considering that AMA-positive cases were 40 of these 511 patients, the study population may not represent the general population of AMA-positive patients. Fifth, the echocardiography results were not included in the multivariate analysis because some patients did not undergo echocardiography. Finally, the incubation period between the appearance of AMA and the onset of the underlying disease could be long-term in asymptomatic cases,[25] causing interpatient variation of baseline data. The prevalence of AMA in healthy or asymptomatic cases may be observed by up to 0.64%.[26,27] In this study, the AMA testing of all included patients was conducted to assess for liver injury, myopathies, or collagen diseases; therefore, accidental positive cases could be few.

Conclusion

The presence of AMA-related noncardiac diseases is an independent risk factor for VTs. AMA induces myocardial damage associated with arrhythmic substrates, probably because of its related mitochondrial damage.

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Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

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