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Inflammatory myopathy associated with anti-mitochondrial antibodies: a distinct phenotype with cardiac involvement

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Abstract

Objective: In the context of clinical evaluations performed on our prospective myositis cohort, we noted a striking association of severe cardiac disease in myositis patients with anti-mitochondrial antibodies. We sought to review all cases of anti-mitochondrial antibody (AMA) associated myositis in our cohort to describe the clinical features of this disease subset.

Methods: We identified 7 patients with confirmed anti-mitochondrial antibodies who presented as an inflammatory myopathy. A retrospective chart review was completed to assess their clinical presentation, laboratory, imaging, electrophysiologic and histopathologic features.

Results: One patient presented with dermatomyositis and six were classified as polymyositis using Bohan and Peter criteria. In all but one patient, a chronic course of muscle involvement was appreciated with an average of 6.5 years of weakness prior to presentation. Muscle atrophy was often noted, as well as atypical findings of scapular winging in 2 of the patients. Muscle biopsies were consistent with immune-mediated necrotizing myopathy in four patients, dermatomyositis in one, polymyositis in one and non-specific or granulomatous myositis in one patient. Changes pointing to mitochondrial alterations were seen in 2 of the 7 patients. Cardiac involvement (including myocarditis, atrial and ventricular arrhythmias and cardiomyopathy), was seen in 5 out of 7 (71%) of the patients, and usually preceded the muscle involvement. Coexisting autoimmune conditions were seen in 3/7 of the patients and included primary biliary cirrhosis, autoimmune hepatitis, psoriasis, and Hashimoto's thyroiditis.

Conclusions: Anti-mitochondrial antibodies identify a distinct inflammatory myopathy phenotype that is frequently associated with chronic skeletal muscle disease and severe cardiac involvement. Early recognition of this rare entity as an immune-mediated process is important due to implications for treatment. We propose that anti-mitochondrial antibody status should be determined in patients with a compatible clinical picture.

Keywords

Anti-mitochondrial antibodies; myositis; cardiomyopathy; arrhythmia; myocarditis

Introduction:

The idiopathic inflammatory myopathies are a group of heterogeneous conditions manifesting with immune-mediated muscle damage. As evidence of the immune-related process, various myositis-specific antibodies as well as myositis-associated antibodies have been described to date, each associated with distinct clinicoserological syndromes[1]. Myositis-specific antibodies are found only in patients with polymyositis (PM), dermatomyositis (DM) and immune-mediated necrotizing myopathies and have a strong association with clinical disease [2,3]. Patients with these specificities frequently have unique features characteristic of that antibody. For example, the presence of ulcerating skin lesions and palmar papules is associated with MDA5 antibodies [4], while patients with a constellation of clinical features that include interstitial lung disease, mechanic's hands and arthritis have anti-synthetase antibodies [5].

Myositis-associated antibodies are less well-defined, and are generally accepted to be those antibodies found in immune and inflammatory myopathies that can also be found in other autoimmune diseases [4]. Examples of myositis-associated antibodies include PM-Scl, Ro52, and U1RNP among others. Having the antibody does not always correlate with the presence of inflammatory muscle disease, and other clinical associations can be seen. These antibodies can be found alone, or in conjunction with other myositis-specific antibodies, and can also have typical clinical presentations. For example in the case of Jo-1 associated interstitial lung disease, the presence of high levels of Ro52 antibodies predicts a more severe acute-onset interstitial lung disease and nonresponse to immunosuppressive treatment [2,6]. Anti-mitochondrial antibodies (AMA) belong in this category.

AMA are most commonly found in association with primary biliary cirrhosis (PBC) [7,8]; however the presence of the antibody has been linked to other autoimmune conditions such as Sjogren's syndrome, scleroderma and autoimmune thyroid disease [9,10]. Inflammatory myopathy occurring in association with AMA is rare, but there is a growing recognition for this clinical entity. We report 7 cases of AMA associated myositis evaluated in a specialty center and describe the clinical characteristics of these patients. This is the largest such cohort reported to date in North America. We note a striking association with cardiac involvement suggesting a distinct phenotype in those patients with this antibody.

Materials and Methods:

Design:

This is a retrospective case series review of patients with AMA and muscle involvement presenting as PM or DM who were evaluated and treated at the Johns Hopkins Myositis Center during the period of 2009–2015. A review of the literature was performed searching for cases of AMA myositis using the terms anti-mitochondrial, myositis, polymyositis, dermatomyositis, myopathy, and primary biliary cirrhosis. References were cross-checked and only cases in English were reviewed.

Patients and data collection:

We identified and reviewed the medical records of those patients who tested positive for AMA. All patients were evaluated as part of routine clinical care at the outpatient Myositis Clinic at the Johns Hopkins Bayview Medical Center in Baltimore, Maryland. Informed consent from the study participants was obtained according to the institutional review board protocol of the Johns Hopkins University. Patients were referred for clinical evaluation on the basis of proximal muscle weakness and elevated muscle enzymes concerning for an inflammatory myositis. All patients had an NCS/EMG and muscle biopsy done as well as laboratory studies with serology and muscle enzymes. Muscle biopsies were prepared routinely using methodology as described previously [11] and reviewed with a neuromuscular pathologist. Routine histochemical and immunohistochemical stains on frozen and paraffin sections were used to assess for necrosis, inflammation, atrophy, fibrosis, and mitochondrial pathology including GT, SDH/COX and NADH stains among others. MRI of the thighs was completed except when the presence of a pacemaker or patient refusal precluded it. Individual patients were clinically assessed with manual muscle strength testing graded by the Medical Research Council scale by the same physician at each visit. Cardiac involvement was assessed by chart review using cardiology notes, imaging, electrocardiograms and histology as available. Cardiac complications were divided into cardiomyopathy, arrhythmias and myocarditis. Cardiomyopathy was defined as abnormalities of the heart muscle or myocardium with dilatation, thickening, or restrictive physiology, usually accompanied by a decreased ejection fraction. Arrhythmias were further subdivided as having conduction blocks, or atrial or ventricular dysrhythmias. Myocarditis was considered present if proven by histology on cardiac biopsy, or as seen with abnormal enhancement on cardiac MRI.

Assessment of antibodies (other than AMA):

Serum samples are routinely collected, aliquoted and banked from all patients evaluated at the Johns Hopkins Myositis Center with probable or definite idiopathic inflammatory myopathy according to the Bohan and Peter criteria [12,13] and from patients with conditions suggesting the diagnosis of myositis. These samples are either collected at the initial or subsequent clinic visits. A myositis autoantibody panel, assayed by the Oklahoma Medical Research Foundation (OMRF), was performed on each serum. This profile uses immunoprecipitation (with HeLa lysates), immunodiffusion (with calf thymus extract), and immunofluorescence (with Hep-2 cells). The antibody specificities tested for included Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, P155/140, RNA POL, TH/TO, U3RNP, MJ, MDA5, PM-Scl, Ku, U1RNP, U2RNP and Ro60. Additional serology was also sent as clinically indicated including for antinuclear antibodies, anti-centromere, anti-smooth muscle and anti-HMGCR antibodies.

Ascertainment of AMA status:

On the OMRF panel, the presence of possible AMA were also reported if bands consistent with this specificity were detected by immunoprecipitation from radiolabeled lysates, or a mitochondrial pattern was noted on indirect immunofluorescence. However, these antibodies are not specifically tested for by the OMRF panel, necessitating confirmation by an

additional assay designed specifically to read out AMAs. For the purposes of screening, all OMRF results during the period of 2009–2015 were reviewed and patients reported to have “possible” AMA were identified for this study. Available sera from these patients were then tested using a commercially available ELISA assay (Inova Diagnostics) that detects AMA (M2 EP, MIT3). Only those patients who were confirmed positive by ELISA were included in this study.

Results:

Out of 1180 patients from the Johns Hopkins Myositis Center who underwent myositis autoantibody testing through OMRF, eight were identified as having potential AMA. Of these, seven were positive by confirmatory ELISA (0.006%). Clinical data, course and treatment were reviewed for these seven patients (supplementary material **and** Table 1). The mean age at diagnosis was 55 years. Patients often displayed a chronic course with respect to their muscle disease, with the average length of disease prior to evaluation at our center being 6.5 years. All patients had weakness, and a significant proportion (6 of 7) also had evidence of muscle atrophy. Atypical findings of scapular winging was seen in 2 of the patients, as well as myotonic discharges on EMG (3 of 7). Although necrosis on muscle biopsy was seen in all but one patient, classification by ENMC criteria [14] yielded one patient classified as DM, four with necrotizing myopathy, one with PM, and one with nonspecific or granulomatous myositis. Two of the seven patients showed mitochondrial alterations on muscle biopsy. One patient presented with typical DM rashes and was classified as DM according to Bohan and Peter criteria, while the other six were PM. Cardiac involvement was seen in 71% (5 of 7) of the patients and was a prominent part of their presentation (see case descriptions in supplemental material).

Discussion:

AMA-associated myositis is not a well-recognized clinical entity. However, there is a growing literature supporting such an association, with at least 24 case reports to date found in English [15–32]. A majority of these cases emerge from East Asia, and a recent comprehensive study from Japan comprising 212 patients with myositis reported a prevalence of 11.3% of AMA-associated myositis in their cohort[33]. In this Japanese study, PM associated with the AMA was characterized by a chronic disease course, muscle atrophy, cardiopulmonary involvement, and the histopathologic feature of granulomatous inflammation. No cases of DM were seen.

In our cohort, a similar picture of chronic muscle disease with AMA myopathy was also appreciated. Muscle involvement appeared subtle initially, sometimes detected solely by asymptomatic CK elevations, usually occurring over the course of months to years. The initial mild muscle symptoms may have played a role in engendering chronicity and delay to diagnosis for many of these patients. By the time patients presented for evaluation, there was often marked muscle atrophy including scapular winging which led to a consideration for a muscular dystrophy. However, genetic testing when suspected was negative. Electromyography confirmed the myopathic process, showing signs of irritability seen with an inflammatory myopathy even after several years of treatment. Other findings such as

myotonic discharges and a concomitant polyneuropathy were also seen. Although myotonic discharges often relate to myotonic dystrophies, they have been seen in the inflammatory myopathies, including necrotizing myopathy [34].

Muscle histopathology most commonly showed a necrotizing myopathy with degenerating and regenerating fibers with or without inflammatory infiltrates. Findings of muscle atrophy and endomysial fibrosis were also noted, speaking to chronicity. In one of our patients, perifascicular atrophy consistent with a histologic picture of DM was also present. Granulomatous inflammation was not a characteristic feature found in our group as compared with the Japanese cohort [33], with only one patient displaying this feature. In the absence of DM-specific findings or granulomatous inflammation, the muscle biopsy findings could lead to a classification of PM or a necrotizing myopathy, depending on classification criteria used. Although the potential for AMA as being another serological marker for immune-mediated necrotizing myopathies has recently been raised [32], it is notable that a spectrum of other histopathologic features have also been seen with this antibody.

Other case reports have also described alterations pointing to muscle mitochondrial pathology with myopathic changes[31]. Findings indicating mitochondrial pathology were present in two of our seven cases. Although such findings are nonspecific, this raises the question as to whether a mitochondrial myopathy is present, occurring through immune-mediated damage to mitochondrial pathways.

A striking clinical feature was the presence of cardiac involvement in the majority of our patients. This took the form of severe conduction abnormalities and arrhythmias, cardiomyopathy, ventricular dilatations, and myocarditis, oftentimes occurring all in the same patient. This was a significant part of the presentation in those who had it, and the cardiac involvement often preceded the onset of muscle disease. Frequently, the arrhythmias had been attributed to other comorbidities such as COPD or thyroid disease, however they were often refractory and required more aggressive intervention with ablation and pacemaker insertions. In the case of cardiomyopathy and myocarditis, treatment with immunosuppression could improve cardiac function. Other reports of AMA-associated myositis have shown a similar pattern to the cardiac disease [18–20,23,28,33], and we believe this cardiac involvement is characteristic of this subgroup. Symptomatic cardiac disease is not a prominent feature of the idiopathic inflammatory myopathies, with myocarditis for example, seen in only 3.6% of anti-synthetase cases in a large study [35].

Interestingly, AMA have been demonstrated in a significant proportion of patients with myocarditis as well as idiopathic dilated cardiomyopathy [36]. For example, in dilated cardiomyopathy, the most abundant protein in the inner mitochondrial membrane has been shown to be an organ specific autoantigen [36]. Functionally active antibodies to this structure have been shown to result in decreased ADP/ATP exchange rate in heart mitochondria by blocking the substrate-binding site of the carrier protein [37,38] leading to an imbalance in energy delivery and demand. This provides a possible mechanism for immunologically mediated dysfunction of the cardiac cell by damage to the mitochondria. Whether these processes are similarly occurring in AMA-associated myositis remains to be seen and deserves further exploration.

Interstitial lung disease was not seen in this group of patients, and inflammatory arthritis was seldom noted. Dysphagia when reported was clinically mild except for the patient with concomitant anti-HMGCR antibodies. DM-specific rashes were seen in one patient, while in another patient without rashes, histopathologic changes of perifascicular atrophy consistent with DM were seen. Both these cases had no known DM-specific antibodies, suggesting that the anti-mitochondrial antibody can be associated with DM as well as PM. Other than the one anti-HMGCR antibody positive patient, no other patients had a myositis-specific antibody. Other coexisting autoimmune conditions were also noted, including primary biliary cirrhosis, autoimmune hepatitis, hypothyroidism and psoriasis. Additional systematic studies comparing anti-mitochondrial disease to other subgroups of myositis across different ethnic cohorts will be necessary to further define this clinical syndrome.

Morbidity was often dictated by the cardiac manifestations as well as muscle weakness. One of the patients reported herein died, but a cause could not be ascertained given lack of autopsy. The trend however, was to improvements seen with immunosuppression, further supporting the immune-mediated process of this disease. Given the severity of the presentation and chronicity of most of the cases however, treatment usually did not reverse the effects of the disease but led to modest improvements/stability.

In summary, we highlight the association of AMA with a phenotype of a chronic inflammatory myopathy and prominent, severe cardiac involvement. Given the increasing evidence for such a distinct clinical entity, we propose that AMA should be added to the growing list of myositis-associated antibodies. They should be searched for in myositis patients with a history of severe cardiac dysrhythmias, cardiomyopathy, or myocarditis, particularly in the absence of a myositis specific antibody. Likewise, if AMA are found in patients with an inflammatory myopathy, screening and monitoring for cardiac disease should be done. As immunosuppressive treatment can lead to improvements in this disease, recognition of this disease entity is of paramount importance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Clinical characteristics of patients with anti-mitochondrial antibody myositis

Age, Sex	62, M	52, M	61, F	64, F	49, F	46, M	51, F
Race	Black	White	White	Black	White	White	White
Duration of weakness prior to first evaluation at JHH (years)	10	6	5	0.3	8	11	5
Muscle symptoms	+	+	+	+	+	+	+
– proximal weakness	+	–	–	–	+	–	–
UE>LE	–	+	+	+	–	+	+
LE>UE	–	–	–	–	–	–	–
UE=LE	–	–	++	+	–	+	++
Neck flexor	+	+	+	+	–	+	+
–muscle atrophy	+	–	–	–	–	+	–
–scapular winging							
Max CK (normal 24–195 U/L)	3024	2800	1213	2100	846	1600	2000
Anti-mitochondrial ab *	112	122	125	46	102	58	107
Associated antibodies	ANA 1:80	–	–	HMGCR Ab	Anti-smooth muscle Ab	Anti-smooth, ANA 1:320 centromere	–
NCS/EMG	+	+	+	+	+	+	+/-
– irritable myopathy	+	+	–	–	–	–	+/-
– neuropathy	–	+	+	–	–	+	–
– myotonic discharges							
Muscle Biopsy	+	+	+	+	+	+	+
–degeneration/regeneration	–	+	–	+	–	–	+
/necrosis	–	–	–	–	–	–	+
– lymphocytic infiltrates	–	–	–	+	–	–	+
– granulomatous inflammation	–	–	–	+	–	–	–
– perivascular inflammation	–	+	–	–	–	–	+
– perifascicular atrophy	–	–	+	+	–	–	–
– fibrosis							
– mitochondrial changes							
MRI	–	N/A	+	+	+	N/A	N/A
– muscle edema	–	N/A	+	–	+	N/A	N/A
– fatty replacement							
Associated autoimmune conditions	–	–	PBC, uveitis, AHepatitis, psoriasis	Psoriasis	–	–	Hashimoto's thyroiditis
Cardiac	+	+	–	–	+	+	+
– cardiomyopathy	+	–	–	–	+	+	+
– arrhythmia	+	–	–	–	–	–	–
heart block	+	+	–	–	+	+	+
atrial tachycardia	–	–	–	–	–	+	–
ventricular fibrillation	+	–	–	–	–	–	+
– myocarditis							
ILD	–	–	–	–	–	–	–
Arthritis	+	–	–	–	+	–	–
Dermatomyositis rash	–	+	–	–	–	–	–
Dysphagia	+	–	+	+	–	+	–
Treatments received	Pred, AZA, RTX	Pred, MTX, IVIG, MMF, RTX	Pred, MMF	Pred, IVIG, MMF	Pred, MTX	Pred, MTX, MMF, IVIG, RTX	Pred, MTX, IVIG, MMF, RTX

Length of follow-up from first visit at JHH; latest known condition	11 y; stable with improved EF	2 y; stable muscle and heart disease	1y; lost to follow-up	3.5y; improved	1y; death of unknown cause	No ff up; By report no improvement in cardiac and muscle disease	2y; worsened heart disease
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* AMA ELISA interpretation: negative <20 U; equivocal 20.1 U-24.9 U; positive >25 U

abbreviations: Pred-prednisone

AZA-azathioprine

MTX-methotrexate

RTX-rituximab

MMF-mycophenolate mofetil

IVIG-intravenous immunoglobulin