Anti-mitochondrial antibodies are not a hallmark of severity in idiopathic inflammatory myopathies

Wladimir Mauhin[a] ; Kuberaka Mariampillai[a] ; Yves Allenbach[a] ; Jean-Luc Charuel[b] ; Lucile Musset[b] ; Olivier Benveniste[a]

A : Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, UMR 974, UPMC, AP-HP, 75013 Paris, France

B : Immunology Department, Hôpital Pitié-Salpêtrière, AP-HP, 75013 Paris, France

Corresponding author: Olivier Benveniste

Hôpital Pitié-Salpêtrière, Médecine Interne et Immunologie Clinique

47-83, boulevard de l'hôpital, 75013 Paris

Olivier.benveniste@aphp.fr

Phone : 33 (0)1 42 17 76 22 Fax : 33 (0)1 42 16 10 58

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Anti-mitochondrial antibodies type 2 (AMA2) are the hallmarks of primary biliary cholangitis (PBC) [1]. AMA2 have also been described in 11.3% of idiopathic inflammatory myopathies (IIM) then associated with cardiac involvement, muscular atrophy and granuloma (table 1) [2].

Screening our *Myositis database* in November 2015, 142 patients had information for AMA2. A muscular lymphoma was excluded. Finally, 11/141 patients (7.8%) were analyzed as AMA2-positive (AMA2+; age at diagnosis 22.7-76.7y.).Proximal muscular weakness was observed in all but two patients with anti-synthetase syndromes. Two patients associated axial involvement, one patient had proximal, axial and distal weakness. Eight AMA2+ patients had difficulties to climb stairs, 6 for walking, 3 for swallowing. Median (interquartile) CK level at diagnosis was 1500U/L (481-8100) in AMA2+ vs 3843 (1050-9000; p=0.20). Among AMA2+, 8/9 had T2-weighted hypersignals on muscular MRI with atrophy in 3 (33.0% vs 52.9%; p=0.19). Cardiac involvement was diagnosed in 4/11 AMA2+ versus 36/122 (p=0.73). One patient exhibited biventricular dilatation with reduced left ventricular function (37%); two others had de novo rhythm troubles and one presented hypokinesia on echography. Cardiac MRI showed hyperT2-weighted signals and gadolinium enhancement in these patients. According to the clinical and pathological ENMC criteria [3], a trend towards higher prevalence of polymyositis was observed in AMA2+ group (5/11 vs 25/130; p=0.06). AMA2+ biopsies revealed no granuloma or particular feature.

AMA2+ patients exhibited less cutaneous manifestations 3/11 vs 79/122 (p=0.02). Specific idiopathic pneumopathy was observed in 3/11 AMA2+ with fibrosis in one, versus 56/108 AMA2- (p=0.2). Two of these three patients had anti-synthetase syndrome associated with cutaneous manifestation in an anti-Jo1 patient. Arthralgia and Raynaud phenomenon were not different between groups. Primary biliary cirrhosis was previously diagnosed in 3 AMA2+ patients without significant association with cardiac involvement. Among AMA2+, five had associated auto-immune disease: lupus, Sjögren, anti-phospholipid, anti-synthetase syndromes, rheumatoid arthritis and Hashimoto's thyroiditis. Among

AMA2+, one had hepatitis C virus associated-hepatocarcinoma, another had polycythemia vera. No other myositis-associated antibody was detected in 2 AMA2+ patients whereas others had anti-signal recognition particle (n=1), anti-HMGCoA-reductase (n=1), anti-Ro52 (n=4), anti-PL7 (n=1), anti-Jo1 (n=1). Among AMA2+ with cardiac involvement, 1 had anti-Ro52, another anti-HMGCoA-reductase antibodies.

AMA2+ patients with cardiac involvement received 1g methylprednisolone infusions (MP; n=3) plus intravenous immunoglobulin (IVIg; n=2), cyclophosphamide (CP; n=3), mycophenolate mofetil (MMF; n=1) and/or plasma-exchanges (EP; n=2), all associated with long-term oral prednisone (1mg/kg/d. then tapered) and methotrexate (MTX; n=3) or azathioprine (AZA; n=1). Two received rituximab as second-line treatment. AMA2+ patients without cardiac involvement received oral prednisone (1mg/kg/d.; n=7/7), IVIg (n=3), MMF (n=1), EP(n=3), MP (n=3), MTX (n=3), AZA (n=1). One patient died from liver failure, 6 improved muscular strength whereas deficit remained stable in 4.

The limitation of this study is the absence of systematic screening for AMA2 in our whole IIMs population. Prospective studies are needed. Interestingly, no IIM was reported in a prospective study of AMA2+ patients (n=1318) [4]. AMA2 seem not associated with cardiac involvement, muscular atrophy or granuloma, neither with a specific pattern of IIM and not appear as a hallmark of severity.

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Table 1. Characteristics of Anti-Mitochondrial antibodies associated myositis.

	Our cohort			*Myositis* database
	AMA2+ n (%)	AMA2- n (%)	*p*	all n (%)
n=	11/141 (7.8)	130/141 (92.2)	-	1098
Mean age at onset (y.)	45.6	46	-	53 (n=492)
Median CK at diagnosis (U/L)	1500	3843	*0.20*	5203.84 (n=441)
Muscle atrophy	3/9 (33.0)	36/68 (52.9)	*0.19*	129/226 (57.07)
Primary Biliary Cholangitis	3/11 (27.3)	nd	*Nd*	ND
Cardiac involvement	4/11 (36.4)	36/122 (29.5)	*0.73*	133 /452 (29.42)
Arthralgia	7/11 (63.6)	57/119 (47.9)	*0.36*	156/446 (34.97)
Cutaneous manifestation	3/11 (27.3)	79/122 (64.8)	*0.02*	243/500 (48.6)
Raynaud phenomenon	5/11 (45.5)	51/120 (42.5)	*1.00*	118/435 (27.12)
Lung involvement	3/11 (27.3)	56/108 (51.8)	*0.20*	143/368 (38.85)
Granuloma	0/11 (0.0)	2/55 (3.6)	*1.00*	7/194 (3.6)
Anti-synthetase syndrome	2/11 (18.2)	26/130 (20.0)	*1.00*	114/1098 (10.38)
Immune Mediated Necrotizing Myopathy	2/11 (18.2)	35/130 (27.0)	*0.73*	127/1098 (11.56)
Dermatomyositis	1/11 (9.1)	22/130 (17.0)	*0.69*	173/1098 (15.75)
Polymyositis	5/11 (45.5)	25/130 (19.0)	*0.06*	197/1098 (17.94)
Inclusion Body Myositis	0/11 (0.0)	17/130 (13.1)	*0.36*	315/1098 (28.68)
Myositis Specific antibodies	4/11 (36.4)	74/124 (59.7)	*0.20*	317/566 (56.01)
anti SRP Ab	1/11 (9.1)	20/121 (16.5)	*1.00*	55 /537 (10.24)
anti HMGCoA reductase Ab	1/11 (9.1)	9/28 (32.1)	*1.00*	51 /105 (48.57)
anti-synthetases Ab	2/11 (18.2)	26/120 (21.6)	*1.00*	112/538 (20.82)
anti-Jo1 Ab	1/11 (9.1)	22/125 (17.6)	*0.69*	99 /562 (17.61)
anti-PL12 Ab	0/11 (0.0)	3/120 (2.5)	*1.00*	6 /538 (1.11)
anti-PL7 Ab	1/11 (9.0)	1/120 (0.8)	*0.16*	7 /538 (1.3)
anti-Ro52 Ab	4/11 (36.4)	56/125 (44.8)	*0.75*	133 /302 (44.04)
anti-SSA60 Ab	1/11 (9.1)	17/124 (13.7)	*1.00*	44 /281 (15.65)