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The diagnostic utility of myositis autoantibody testing for predicting the risk of cancer-associated myositis

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ABSTRACT

Objectives: There is a known association between myositis and cancer. The risk is greater in dermatomyositis than polymyositis, although reliable methods to predict cancer risk in specific myositis patients are not presently available. This study was undertaken to determine whether risk of developing cancer in myositis is predictable by antibody profiling.

Methods: A cross-sectional study of UK Caucasian adults with polymyositis (PM, n=109), dermatomyositis (DM, n=103) and connective tissue disease overlap (myositis/CTD-overlap, n=70). Patients were tested for a comprehensive range of myositis-specific/associated autoantibodies (MSA/MAAs). Sensitivity and specificity analyses were performed for optimal identification of cancer risk.

Results: Sixteen patients had cancer-associated myositis (CAM) (15 DM, 1 myositis/CTD-overlap). CAM patients were older at disease onset, and patients without MSA/MAAs on 'routine' laboratory testing (negative for anti-Jo-1, -PM-Scl, -U1-RNP, -U3-RNP, -Ku antibodies) had a significantly increased risk of CAM. Possession of the antibody (Ab) against 155kDa and 140kDa protein specificities (anti-155/140 Ab) represented a significant risk factor for CAM, this doublet being found exclusively in DM. A positive anti-155/140 Ab result proved highly specific, moderately sensitive, with high negative predictive value (NPV) for CAM. A 'negative routine myositis Ab panel' result was highly sensitive, with high NPV for CAM. The combination of these two approaches was 94% sensitive, detecting 15/16 CAM, with 100% sensitivity and NPV in DM.

Conclusions: These results may help clinicians predict which myositis patients are at greater risk of developing cancer, thus identifying those requiring aggressive diagnostic evaluation and intensive cancer surveillance at myositis onset and follow-up.

Keywords: polymyositis, dermatomyositis, cancer, sensitivity and specificity, autoantibodies

INTRODUCTION

Evidence for a significant myositis-cancer association has come from case reports, case-control and population-based cohort studies which have demonstrated a greater cancer risk in dermatomyositis (DM) compared to polymyositis (PM).[1-4] Clinicians must therefore determine the degree of testing necessary to assess for the presence of cancer at myositis onset, and the frequency/intensity of repeat testing thereafter. Reliable methods to predict cancer risk in myositis patients would significantly benefit clinicians managing such patients. Case-control studies have attempted to identify serological characteristics of CAM patients, compared to those without cancers, but serological profiles predictive of CAM have not emerged.[5;6]

Myositis-specific or myositis-associated autoantibodies (MSAs/MAAs) are present in about 40% of patients with myositis. These antibodies (Abs) define distinct clinical subsets,[7-10] suggesting that they may play an active role in the immunopathogenesis of myositis.[11-13] A novel Ab, directed against a 155kDa protein, has been reported in DM patients with or without CAM where other MSAs/MAAs were not detected. This new Ab occurs as a 'doublet' with a second Ab directed against a 140kDa protein (anti-155/140 Ab).[14;15] In a large cohort of Caucasian myositis patients, we examined the association between anti-155/140 Ab and CAM, as well as the development of other myositis phenotypic features. The authors were conscious of the limitations of Ab detection repertoires in commercially available test kits used by clinical immunology laboratories to assess known MSAs/MAAs, including the newly identified anti-155/140 Ab. In view of such limitations, the ability of routine MSA/MAA testing to predict or exclude CAM was also assessed.

METHODS

Study design: A cross-sectional study of UK Caucasian patients with PM, DM and myositis in overlap with another connective tissue disease (myositis/CTD-overlap).

Cases: Between 1999-2004, a UK-wide collaboration of 56 rheumatologists and 4 neurologists comprising the Adult Onset Myositis Immunogenetic Collaboration (AOMIC, for details see appendix in [9]) recruited Caucasian myositis patients, aged 18 years or older at disease onset,[9] from clinical units in 40 teaching and district general hospitals. The inclusion criteria for all PM and DM patients was probable or definite disease, according to the Bohan and Peter criteria.[16;17] For myositis/CTD-overlap patients, use of these criteria is problematic, as myositis is often diagnosed less rigorously in the context of another CTD (likely reflecting the lack of electromyography (EMG) and muscle histology expertise in UK non-teaching centres). Thus, 17 of the 70 (24%) myositis/CTD-overlap patients were included for analysis if they fulfilled all of the following: 1) met published criteria for their primary CTD[18-22] or mixed connective tissue disease (MCTD);[23] 2) possessed at least two of four Bohan and Peter criteria (proximal muscle weakness, elevated muscle enzymes, characteristic myopathic EMG changes, diagnostic muscle biopsy); 3) possessed at least one MSA/MAA. The remaining 53 myositis/CTD-overlap patients all fulfilled criteria for their primary disease/MCTD and probable/definite myositis according to Bohan and Peter. A standardised one page clinical data collection proforma facilitated recruitment, detailing demographics and basic individual clinical details. Patients' written consent to participate was obtained according to the Declaration of Helsinki, ethical approval having been gained locally at each participating centre.

Reference standard, cancer-associated myositis: CAM was defined as cancer occurring in myositis patients within three years of myositis diagnosis (as per the modified Bohan and Peter classification[6]). Using relevant investigations, each collaborating physician confirmed or excluded (in their opinion) the presence of CAM. The average duration of myositis at the time of patient recruitment was three years, and over 90% of recruited patients to date have been followed for longer than three years, including clinical reassessments for cancer development.

Serological typing: At the time of recruitment, plasma was obtained from all patients for the determination of MSAs and MAAs, and stored at -80°C. Determination of MSAs (anti-synthetases: -Jo-1, -PL-7, -PL-12, -EJ, -OJ, -KS; anti-Mi-2, anti-SRP, anti-155/140) and MAAs (anti-PM-Scl, -Ku, -U1-RNP, -U3-RNP) was performed in a dedicated research laboratory blinded to all clinical data including diagnoses, prior MSA/MAA results and CAM status, as previously described.[9] Determination of the anti-155/140 Ab was accomplished by comparison of the apparent molecular weights of the immunoprecipitated ^{35}S methionine-labelled proteins with similarly sized molecular weight markers visualized by autoradiography on 6% sodium dodecyl sulphate polyacrylamide gels. This technology was analogous to that already published for identification of the anti-155/140 Ab.[14;15]

Statistical analyses: Individual associations were derived from 2 x 2 contingency tables. Probabilities were calculated using Fisher's exact test. Data were expressed as odds ratios (OR), given with exact 95% confidence intervals (CI). The diagnostic accuracy of the results, regarding detecting or excluding CAM, was assessed by the calculation of positive and negative predictive values, sensitivity, specificity and the receiver-operator characteristic (ROC) area (sensitivity + specificity / 2), with diagnosis of CAM as the reference standard. Unless otherwise stated, the statistical package Stata (Release 8, Stata Corp, College Station, TX, USA) was used to perform the statistical analysis.

RESULTS

Demographics: The 282 patients recruited for the study included 109 PM (68% females), 103 DM (70% females) and 70 myositis/CTD-overlap (77% females). The myositis/CTD-overlap patients had the following primary diagnoses: 45 systemic sclerosis (SSc), 9 MCTD, 7 Sjögren syndrome, 7 systemic lupus erythematosus (SLE) and 2 rheumatoid arthritis (RA). A total of 25 patients had a detectable cancer (Table 1), and of these, 15/103 (15%) had DM, 1/71 (1%) myositis/CTD-overlap while no PM patients fulfilled the criteria for CAM. The cancer sites in the 16 CAM patients were as follows: 4 breast, 3 each of gynaecological, lymphoma and gastrointestinal, 2 bladder and 1 lung. Eleven of the 16 CAM patients developed their malignancy within one year of myositis onset. The proportion of females was non-significantly higher in non-CAM (72%) compared to CAM (56%) patients (p=0.2). The median age at myositis-onset was higher in the CAM group compared to the non-CAM group (CAM 58 years *vs.* non-CAM 48 years, p=0.06). No between-gender differences were observed in the age distribution of the CAM/non-CAM subgroups.

Autoantibody frequencies: The frequencies and phenotypic associations of the MSA/MAAs detected are shown in Table 2. The autoAb frequencies in PM/DM (except those for the anti-155/140 Ab), have been previously reported.[9] In the myositis/CTD-overlap group, anti-U1-RNP (27%) and anti-PM-Scl (27%) Abs were most common, reflecting the frequency of MCTD and SSc respectively. The known anti-synthetase-interstitial lung disease (ILD) association[9] was confirmed in the myositis/CTD-overlap group (presence of ILD in myositis/CTD-overlap, 6/10 (60%) anti-synthetase positive *vs.* 14/61 anti-synthetase negative (22%), OR 5.2, 95% CI 1.0-27.7, p=0.02). No myositis/CTD-overlap patients were observed with either anti-Mi-2 or -SRP Abs.

Characteristics of patients with anti-155/140 Abs: Anti-155/140 Abs were exclusively found in DM patients (overall frequency of 18.4%). There was a higher proportion of females in anti-155/140 Ab positive (84%) *vs.* negative (70%) patients (p=0.2). There was no significant difference in the median age of myositis-onset between anti-155/140 Ab positive and negative patients. ILD was not detected in any anti-155/140 Ab positive patient, or in any CAM patient without anti-155/140 Ab. The Ab results stratified by CAM status are summarised in Table 3. In contrast to the noticeable lack of other detectable Abs in the CAM group, anti-155/140 Abs were present in 8/16 (50%) of these patients, but in only 11/266 (4%) of the non-CAM group. The risk of CAM was therefore significantly increased in anti-155/140 Ab positive compared to anti-155/140 Ab negative patients (see Table 3). This risk was still present in the DM group alone (OR 8.0, 95% CI 2.0-31.1, p=0.0009). The other Abs detected in CAM included anti-KS (one patient), anti-U1-RNP (two patients) and anti-Mi-2 (two patients). The anti-KS and anti-U1-RNP positive CAM patients both also possessed anti-155/140 Abs, as did an anti-Jo-1 positive non-CAM patient. Of the 8 anti-155/140 Ab positive patients with CAM, 7 developed their cancers within a year of their DM diagnosis. The anti-155/140 Ab positive patients without CAM (n=11) have been followed up for a median of 9 years after myositis diagnosis, and at the time of writing, none have developed malignancy. The remaining six CAM patients possessed no detectable Abs**.**

Utility of Ab testing for prediction of CAM: When all of the research-laboratory-detected Abs were considered, including anti-155/140 Ab, the risk of CAM was not increased in Ab negative patients (5/111 (5%) Ab negative *vs.* 11/171 (6%) in Ab positive patients, p=0.6). Our local hospital-based immunology laboratory tests for anti-Jo-1, -U1-RNP, -U3-RNP, -Ku and -PM-Scl Abs. Thus, anti-Mi-2, -SRP, -155/140 Abs and the remaining anti-synthetases would all remain undetected. Assuming only routine, hospital-based Ab testing was undertaken, 14/160 (9%) patients without routinely detected Abs would have CAM *vs.* 2/122 (2%) patients with a routinely detected Ab (OR 5.8, 95% CI 1.3-52.9, p=0.01). Within the DM group, the number of CAM patients that would be detected with routine methods was 14/67 (21%) no Ab detected *vs.* 1/36 (3%) Ab detected (OR 9.2, 95% CI 1.3-401.8, p=0.02).

The diagnostic accuracy of Ab testing was ascertained by performing sensitivity and specificity analyses (Table 4). Routine laboratory Ab testing was assessed, with 'Ab-negative' status, anti-155/140 Ab positive, or a combination of the two strategies classified as a positive outcome. An 'Ab negative' result on routine testing was highly sensitive for CAM detection, demonstrating a high negative predictive value (NPV). Testing for anti-155/140 Abs alone was 50% sensitive for the detection of CAM (half of the CAM patients possessed this Ab), and with a 42% positive predictive value (PPV) (58% false positive rate). However, the anti-155/140 Ab test was 96% specific (most non-CAM patients were negative for this Ab) and demonstrated a high NPV (97% of patients without anti-155/140 Ab did not have CAM). Finally, in combining the two strategies, no routinely detected Abs or anti-155/140 Ab positivity, there was 94% sensitivity and 99% NPV (indicating that only 1% with a routinely detected Ab or a negative anti-155/140 Ab had CAM). When the DM group was analysed alone, this combined strategy yielded 100% sensitivity and NPV. For all three approaches in Table 4, the ROC area was similar at a level of about 0.7. The results also produced similar results when the cut-off for CAM was increased from three to four years, although sensitivity for the anti-155/140 Ab test alone was reduced to 44%, and a longer cut-off further reduced sensitivity across the three strategies.

DISCUSSION

The results from this study confirm previously reported findings that the risk of CAM is clearly greater in DM compared to other myositis subsets, and in patients with an older age at myositis onset. The major study objective was to assess the utility of autoantibody testing to predict the risk of CAM. The 'Ab-negative' result on 'routine' Ab testing demonstrates very high sensitivity and NPV, and anti-155/140 Ab testing alone provides an excellent NPV and specificity. The combination of either a routine 'Ab-negative' result or a positive anti-155/140 Ab result produces higher sensitivity and NPV, with values of 100% within the DM group. It should be noted that some laboratories outside of the UK may routinely test for anti-Mi-2. However, the small number of anti-Mi-2 Ab positive CAM patients presented here does not clarify if this Ab also represents a cancer risk. A recent large US Caucasian myositis study suggested low anti-Mi-2 frequencies in CAM,[10] although a European study suggested that cancer risk was increased, but only in those myositis patients possessing the N-terminal fragment of the Mi-2 antigen.[24] The remaining CAM patients without a defined Ab may possess other, and as yet unidentified, Abs.

The results from this study also further defines myositis clinical phenotypes according to MSA/MAA status, as anti-Jo-1 positive patients appear at risk of developing ILD but not CAM. This result strengthens previous findings which suggest that anti-155/140 Ab positivity and ILD are mutually exclusive,[14;15] and is thus of considerable clinical interest to physicians in deciding the extent of cancer screening in individual myositis patients. Two patients in the current study did have anti-synthetases and anti-155/140 Abs but to date, neither have developed ILD. The well documented anti-synthetase-ILD association in PM/DM[7;9] is also confirmed here in a myositis/CTD-overlap subset, showing that the risk of ILD appears to be driven by an anti-synthetase association rather than by the clinical myositis subset. In contrast, both CAM and anti-155/140 Ab positivity appear exclusive to DM. Thus, analogous to the anti-Mi-2 Ab, the anti-155/140 Ab should also be considered as DM-specific.

The anti-155/140 Ab was originally described in both juvenile and adult DM patients by Targoff *et al*.[25] Six of eight CAM patients in their cohort had anti-155/140 Abs, and none of 16 adult IIM patients with the Ab had ILD [14]. The Ab has also been described by Kaji *et al*,[15] who detected an anti-155/140 Ab doublet in 7/52 DM patients, five of whom had cancer without ILD. The identity of the 155/140 kDa protein target is proposed to be transcriptional intermediary factor 1-gamma.[26]

There are a number of potential problems with this study which require discussion. Due to the limited data collection, information is unavailable pertaining to potential cancer-related risk factors, e.g. cytotoxic therapy, treatment response or smoking habits. Moreover, we do not have precise details of investigations used to exclude CAM at myositis onset which were not standardised across AOMIC centres. Inability to capture such data was due to use of a basic clinical proforma, necessitated by preliminary use of a more comprehensive proforma which initially deterred collaborators from patient recruitment. As the current study was cross-sectional, the overall number of detected cancers may be an underestimate. However, as the median duration of disease at data-capture was three years, according to the definition of CAM used,[6] most CAM cases would have become overt in our cohort. The temporal aspects of the CAM definition used is based on previous studies showing that newly diagnosed cases become less frequent after the first three years following myositis diagnosis,[1-4] and therefore excludes patients with cancer diagnosed thereafter. Clearly, the longer these myositis patients are followed up, the greater the likelihood is for the development of myositis-unrelated cancers, highlighting the current difficulty in defining accurate CAM temporal limits. Routine Ab testing is not foolproof for detecting CAM and development of a commercially viable test for anti-155/140 Ab is not on the horizon, therefore physicians caring for myositis patients must remain vigilant regarding cancer development with

intensive yearly surveillance for three to four years after myositis-onset. Before these results can be applied clinically, they require confirmation in a large independent trial with prospective follow up, the results of which would further aid in an accurate definition of CAM.

Despite these limitations, the results of this study demonstrate autoantibody differences between CAM and non-CAM patients, where an absence of MSA/MAAs on routine testing clearly increases the likelihood of CAM, especially in DM. The addition of anti-155/140 testing would considerably aid the prediction of CAM, highlighting the importance of being able to routinely test this Ab in myositis patients. Further validation is needed, but from a clinical perspective one can conclude that when routine myositis Ab testing in adult myositis patients is negative, extra vigilance is required in screening for co-existent cancers.

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COMPETING INTERESTS

Nil

Table 1: Characteristics of myositis patients developing cancer

ID	Gender	Diagnosis	Detected antibodies	Age at myositis onset /years	Site of malignancy	Time of cancer onset relative to myositis onset /years	Classified as CAM
1	M	DM	-	19	Lymphoma	Same time	Yes
2	F	DM	155/140	37	Breast	0.8	Yes
3	F	DM	KS, 155/40	47	Lymphoma	2	Yes
4	M	DM	-	48	Lymphoma	3	Yes
5	F	DM	-	52	Ovarian	1	Yes
6	M	DM	Mi-2	52	Colon	Same time	Yes
7	F	DM	155/140	57	Breast	2	Yes
8	M	DM	Mi-2	59	Caecum	2	Yes
9	F	DM	155/140	59	Breast	1	Yes
10	F	DM	155/140	60	Uterine	Same time	Yes
11	F	DM	155/140	63	Ovarian	Same time	Yes
12	F	DM	155/140	63	Oesophagus	0.3	Yes
13	M	DM	-	63	Bladder	3	Yes
14	M	DM	U1-RNP,155/140	69	Bladder	-0.9	Yes
15	F	DM	-	73	Breast	Same time	Yes
16	M	MCTD	U1-RNP	46	Lung	Same time	Yes
17	F	PM	-	35	Paget's nipple	4	No
18	M	PM	Jo-1	35	Lymphoma	7	No
19	F	PM	Jo-1	48	Breast	5	No
20	M	PM	Jo-1	54	Lung	12	No
21	F	PM	-	58	Breast	5	No
22	M	PM	-	68	Colon	4	No
23	F	SSc overlap	Jo-1	18	Vulva	7	No
24	M	SSc overlap	PM-Scl	40	Colon	10	No
25	F	SSc overlap	-	46	Lymphoma	8	No
26	F	SSc overlap	PM-Scl	49	Pancreas	8	No

Key: PM=polymyositis, DM=dermatomyositis, SSc=systemic sclerosis, MCTD=mixed connective tissue disease, CAM=cancer-associated myositis

Table 2: Serological frequencies in myositis subgroups

	n (%)		
	Polymyositis	Dermatomyositis	Myositis/CTD - overlap
Autoantibody status	(n=109)	(n=103)	(n=70)
Myositis-specific autoAbs:			
Jo-1	27 (24.8)	23 (22.3)	8 (11.4)
PL-7	1 (0.9)	0	0
PL-12	0	1 (1.0)	0
EJ	0	1 (1.0)	0
OJ	1 (0.9)	1 (1.0)	1 (1.4)
KS	1 (0.9)	1 (1.0)	0
Mi-2	1 (0.9)	17 (16.5)	0
SRP	5 (4.6)	2 (1.9)	0
155/140	0	19 (18.4)	0
Myositis-associated autoAbs			
U1-RNP	5 (4.6)	10 (9.7)	19 (27.1)
U3-RNP	0	2 (1.9)	2 (2.9)
Ku	0	2 (1.9)	3 (4.3)
PM-Scl	5 (4.6)	5 (4.8)	19 (27.1)
None of the above autoAbs			
	63 (57.8)	30 (29.1)	20 (28.6)

Key for Tables 1 and 2: AutoAbs=autoantibodies, SRP=signal recognition particle, CTD=connective tissue disease. Numbers do not add up to totals due to presence of patients with multiple autoantibodies.

Table 3: Serological frequencies in overall non-CAM and CAM groups

	n (%)	
	Non-CAM	CAM
Autoantibody status	(n=266)	(n=16)
Myositis-specific Abs		
Jo-1	58 (21.8)	0
PL-7	1 (0.4)	0
PL-12	1 (0.4)	0
EJ	1 (0.4)	0
OJ	3 (1.1)	0
KS	1 (0.4)	1 (6.2)
Mi-2	16 (6.0)	2 (12.5)
SRP	7 (2.6)	0
155/140	11 (4.1)	8 (50.0)
Myositis-associated Abs		
U1-RNP	32 (12.0)	2 (12.5)
U3-RNP	4 (1.5)	0
Ku	5 (1.9)	0
PM-Scl	29 (10.9)	0
None of the above autoAbs		
	106 (39.8)	5 (31.2)

CAM=cancer associated myositis
Numbers do not add up to totals due to presence of patients with multiple autoantibodies
Risk of CAM: anti-155/140 Ab positive *vs.* anti-155/140 Ab negative, p=0.0009, odds ratio 23.2, 95% confidence interval 6.1-84.5.

Table 4: Utility of diagnostic serology tests to predict cancer-associated myositis

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	ROC Area[1]
Detection of anti-155/140 Ab	50.0 (24.7-75.3)	95.9 (92.7-97.9)	42.1 (20.3-66.5)	97.0 (94.1-98.7)	0.73 (0.60-0.86)
Negative Ab result on hospital-based routine immunology testing[2]	87.5 (61.7-98.4)	45.1 (39.0-51.3)	8.7 (4.9-14.2)	98.4 (94.2-99.8)	0.66 (0.57-0.75)
Negative Ab result on hospital-based routine immunology testing and detection of anti-155/140 Ab	93.8 (69.8-99.8)	44.7 (38.7-50.9)	9.3 (5.3-14.8)	99.2 (95.4-100)	0.69 (0.62-0.76)

Ab=antibody, ROC=receiver-operator characteristic

[1]Sensitivity + specificity/2

[2]Includes testing for anti-Jo-1, -Ku, -PM-Scl, -U1-RNP, -U3-RNP

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