EXTENDED REPORT

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

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

Methods: A cross-sectional study of UK Caucasian adults with PM (n = 109), 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. Sensitivity and specificity analyses were performed for the 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 myositis-specific/associated autoantibodies on "routine" laboratory testing (negative for anti-Jo-1, anti-PM-Scl, anti-U1-RNP, anti-U3-RNP, anti-Ku antibodies) had a significantly increased risk of CAM. Possession of the antibody against 155 kDa and 140 kDa protein specificities (anti-155/140 antibody) represented a significant risk factor for CAM, and was found exclusively in DM. A positive anti-155/140 antibody result proved highly specific, moderately sensitive, with high negative predictive value for CAM. A "negative routine myositis antibody panel" result was highly sensitive, with high negative predictive value for CAM. The combination of these two approaches was 94% sensitive, detecting 15 of 16 CAM, with 100% sensitivity and negative predictive value in DM.

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

E vidence 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 with 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 patients with myositis would significantly benefit clinicians managing such patients. Case–control studies have attempted to identify serological characteristics of cancer-associated myositis (CAM) patients, compared with 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 define distinct clinical subsets,[7–10] suggesting that they may play an active role in the immuno-pathogenesis of myositis.[11–13] A novel antibody, directed against a 155 kDa protein, has been reported in DM patients with or without CAM where other MSAs/MAAs were not detected. This new antibody occurs as a "doublet" with a second antibody directed against a 140 kDa protein (anti-155/140 antibody).[14 15] In a large cohort of Caucasian patients with myositis, we examined the association between anti-155/140 antibody and CAM, as well as the development of other myositis phenotypic features. The authors were conscious of the limitations of antibody detection repertoires in commercially available test kits used by clinical immunology laboratories to assess known MSAs/MAAs, including the newly identified anti-155/140 antibody. In view of such limitations, the ability of routine MSA/MAA testing to predict or exclude CAM was also assessed.

METHODS

Study design

This was a cross-sectional study of UK Caucasian patients with PM and DM, and myositis in overlap with another connective tissue disease (myositis/CTD-overlap).

Cases

Between 1999 and 2004, the Adult Onset Myositis Immunogenetic Collaboration (AOMIC, comprising a UK-wide collaboration of 56 rheumatologists and four neurologists; for details see appendix in[9]) recruited Caucasian patients with myositis, 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 patients with myositis/CTD-overlap, use of these criteria is problematic, as myositis is often diagnosed less rigorously in the context of another CTD (likely reflecting the lack of expertise of electromyography and muscle histology 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: (a) met published criteria for their primary CTD[18–22] or mixed connective tissue disease (MCTD);[23] (b) possessed at least two of four Bohan and Peter criteria (proximal muscle weakness, elevated muscle enzymes,

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Abbreviations: AOMIC, Adult Onset Myositis Immunogenetic Collaboration; CAM, cancer-associated myositis; CI, confidence intervals; CTD, connective tissue disease; DM, dermatomyositis; ILD, interstitial lung disease; MAA, myositis-associated autoantibody; MCTD, mixed connective tissue disease; MSA, myositis-specific autoantibody; NPV, negative predictive value; OR, odds ratios; PM, polymyositis; PPV, positive predictive value

characteristic myopathic electromyography changes, diagnostic muscle biopsy); (c) 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 patients with myositis within 3 years of diagnosing myositis (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 3 years, and over 90% of recruited patients to date have been followed for longer than 3 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℃. Determination of MSAs (anti-synthetases: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS; anti-Mi-2, anti-SRP, anti-155/140) and MAAs (anti-PM-Scl, anti-Ku, anti-U1-RNP, anti-U3-RNP) was performed in a dedicated research laboratory blinded to all clinical data, including diagnoses, previous MSA/MAA results and CAM status, as previously described.[9] Anti-155/140 antibody was determined by comparing the apparent molecular weights of 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 antibody.[14 15]

Statistical analyses

Individual associations were derived from 2×2 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 calculating positive predictive values (PPVs) and negative predictive values (NPVs), sensitivity, specificity and the receiver-operator characteristic area (sensitivity + specificity/2); the diagnosis of CAM was the reference standard. Unless otherwise stated, the statistical package Stata (Release 8, Stata Corp, College Station, Texas, USA) was used to perform the statistical analysis.

RESULTS
Demographics

In total, 282 patients were recruited for the study: 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: systemic sclerosis (45), MCTD (nine), Sjögren syndrome (seven), systemic lupus erythematosus (seven) and rheumatoid arthritis (two). A total of 26 patients had a detectable cancer (table 1) with 16 classified as CAM. Fifteen of 103 (15%) patients with DM, one of 71 (1%) with myositis/CTD-overlap and no patients with PM fulfilled the criteria for CAM. The cancer sites in the 16 patients with CAM were as follows: breast (four), gynaecological (three), lymphoma (three), gastrointestinal (three), bladder (two) and

lung (one). Eleven of the 16 CAM patients developed their malignancy within 1 year of the onset of myositis. The proportion of females was non-significantly higher in non-CAM (72%) compared with patients with CAM (56%) (p = 0.2). The median age at myositis onset was higher in the CAM group compared with the non-CAM group (CAM 58 years versus 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 autoantibody frequencies in PM/DM (except those for the anti-155/140 antibody), have been previously reported.[9] In the myositis/CTD-overlap group, anti-U1-RNP (27%) and anti-PM-Scl (27%) antibodies were most common, reflecting the frequency of MCTD and systemic sclerosis 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, six of 10 (60%) anti-synthetase positive versus 14 of 61 anti-synthetase negative (22%), OR 5.2, 95% CI 1.0 to 27.7, p = 0.02). No patients with myositis/CTD-overlap were observed with either anti-Mi-2 or anti-SRP antibodies.

Characteristics of patients with anti-155/140 antibodies

Anti-155/140 antibodies were exclusively found in DM patients (overall frequency of 18.4%). There was a higher proportion of females in anti-155/140 antibody positive (84%) versus negative (70%) patients (p = 0.2). There was no significant difference in the median age of myositis onset between patients who were anti-155/140 antibody positive and negative. ILD was detected

Table 1 Characteristics of patients with myositis 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

PM, polymyositis; DM, dermatomyositis; SSc, systemic sclerosis; MCTD, mixed connective tissue disease; CAM, cancer-associated myositis.

Table 2 Serological frequencies in myositis subgroups

Autoantibody status	n (%)		
	Polymyositis (n = 109)	Dermatomyositis (n = 103)	Myositis/CTD-overlap (n = 70)
Myositis-specific autoantibodies:			
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 autoantibodies			
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 autoantibodies	63 (57.8)	30 (29.1)	20 (28.6)

SRP, signal recognition particle; CTD, connective tissue disease. Numbers do not add up to totals due to presence of patients with multiple autoantibodies.

in only one patient with CAM who was also anti-155/140 antibody positive. The antibody results stratified by CAM status are summarised in table 3. In contrast to the noticeable lack of other detectable antibodies in the CAM group, anti-155/140 antibodies were present in eight of 16 (50%) of these patients, but in only 11 of 266 (4%) of the non-CAM group. The risk of CAM was therefore significantly increased in patients who were anti-155/140 antibody positive compared with those who were anti-155/140 antibody negative (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 antibodies detected in CAM included anti-KS (one patient), anti-U1-RNP (two patients) and anti-Mi-2 (two patients). The patients with CAM who were anti-KS-and anti-U1-RNP-positive both also possessed anti-155/140 antibodies, as did a patient in the non-CAM group who was anti-Jo-1 positive. Of the eight patients with CAM who were anti-155/140 antibody positive, seven developed their cancers within a year of their DM diagnosis. The anti-155/140 antibody positive patients without CAM (n = 11) have been followed up for a median of 9 years after being diagnosed with myositis, and at the time of writing, none have developed malignancy. The remaining six patients with CAM possessed no detectable antibodies.

Efficacy of antibody testing for prediction of cancer-associated myositis

When all of the research-laboratory-detected antibodies were considered, including anti-155/140 antibody, the risk of CAM was not increased in patients who were antibody negative (five of 111 (5%) patients were antibody negative versus 11 of 171 (6%) patients who were antibody positive, p = 0.6). Our local hospital-based immunology laboratory tests for anti-Jo-1, anti-U1-RNP, anti-U3-RNP, anti-Ku and anti-PM-Scl antibodies. Thus, anti-Mi-2, anti-SRP, anti-155/140 antibodies and the remaining anti-synthetases would all remain undetected. Assuming only routine, hospital-based antibody testing was undertaken, 14 of 160 (9%) patients without routinely detected antibodies would have CAM versus two of 122 (2%) patients with a routinely detected antibody (OR 5.8, 95% CI 1.3 to 52.9, p = 0.01). In DM 14 of 67 (21%) patients without a routinely detected antibody had CAM, versus one of 36 (3%) with a

routinely detected antibody (OR 9.2, 95% CI 1.3 to 401.8, p = 0.02).

The diagnostic accuracy of antibody testing was ascertained by performing sensitivity and specificity analyses (table 4). Routine laboratory antibody testing was assessed, with "antibody-negative" status, anti-155/140 antibody positive, or a combination of the two strategies classified as a positive outcome. An "antibody negative" result on routine testing was highly sensitive for CAM detection, demonstrating a high NPV. Testing for anti-155/140 antibodies alone was 50% sensitive for the detection of CAM (half of the CAM patients possessed this antibody), and with a 42% PPV (58% false positive rate). However, the anti-155/140 antibody test was 96% specific (most non-CAM patients were negative for this antibody) and demonstrated a high NPV (97% of patients without anti-155/140 antibody did not have CAM). Finally, in combining the two strategies, no routinely detected antibodies or anti-155/140 antibody positivity, there was 94% sensitivity and 99% NPV (indicating that only 1% with a routinely detected antibody or a negative anti-155/140 antibody 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 receiver-operator characteristic 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 3 to 4 years, although sensitivity for the anti-155/140 antibody 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 with other myositis subsets, and in patients with an older age at myositis onset. The major study objective was to assess the efficacy of autoantibody testing to predict the risk of CAM. The "antibody-negative" result on "routine" antibody testing demonstrates very high sensitivity and NPV, and anti-155/140 antibody testing alone provides an excellent NPV and specificity. The combination of either a routine "antibody-negative" result or a positive anti-155/140 antibody 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 patients with CAM who were anti-Mi-2 antibody positive in this study does not clarify if this antibody also represents a cancer risk. A recent large US Caucasian myositis study suggested low anti-Mi-2 frequencies in CAM;[10] however, a European study suggested that cancer risk was increased, but only in those patients with myositis possessing the N-terminal fragment of the Mi-2 antigen.[24] The remaining patients with CAM without a defined antibody may possess other, and as yet unidentified, antibodies.

The results from this study also further define myositis clinical phenotypes according to MSA/MAA status, as patients that were anti-Jo-1-positive appear at risk of developing ILD but not CAM. This result strengthens previous findings that suggest anti-155/140 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 patients with myositis. Two patients in the current study did have anti-synthetases and anti-155/140 antibodies, 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 antibody positivity appear exclusive to

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

Autoantibody status	n (%)	
	Non-CAM (n = 266)	CAM (n = 16)
Myositis-specific antibodies		
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 antibodies		
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 autoantibodies	106 (39.8)	5 (31.2)

CAM, cancer-associated myositis.
Numbers do not add up to totals due to the presence of patients with multiple autoantibodies.
Risk of CAM: anti-155/140 antibody positive versus anti-155/140 antibody 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*
Detection of anti-155/140 antibody	50.0	95.9	42.1	97.0	0.73
Negative antibody result on hospital-based routine immunology testing†	87.5	45.1	8.7	98.4	0.66
Negative antibody result on hospital-based routine immunology testing and detection of anti-155/140 antibody	93.8	44.7	9.3	99.2	0.69

ROC, receiver-operator characteristic.
*Sensitivity + specificity/2.
†Includes testing for anti-Jo-1, anti-Ku, anti-PM-Scl, anti-U1-RNP, anti-U3-RNP.

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 patients with and without CAM, 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 for this antibody in patients with myositis. Further validation is needed; however, from a clinical perspective one can conclude that when routine myositis antibody testing in adult patients with myositis is negative, extra vigilance is required in screening for coexistent cancers.

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DM. Thus, analogous to the anti-Mi-2 antibody, the anti-155/140 antibody should also be considered as DM specific.

The anti-155/140 antibody was originally described in both juvenile and adult patients with DM by Targoff et al.[25] Six of eight patients with CAM in their cohort had anti-155/140 antibodies, and none of 16 adult patients with idiopathic inflammatory myopathy with the antibody had ILD.[14] The antibody has also been described by Kaji et al,[15] who detected an anti-155/140 antibody doublet in seven of 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-γ.[26]

There are a number of potential problems with this study that require discussion. Owing to the limited data collection, information is unavailable pertaining to potential cancer-related risk factors, eg, cytotoxic therapy, treatment response or smoking habits. Moreover, we do not have precise details of investigations used to exclude CAM at myositis onset that were not standardised across AOMIC centres. Inability to capture such data was due to the use of a basic clinical proforma, necessitated by preliminary use of more comprehensive proformas, which initially deterred collaborators from patient recruitment. As the current study was cross-sectional, the overall number of detected cancers may be underestimated. However, as the median duration of disease at data capture was 3 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 3 years following myositis diagnosis,[1–4] and therefore excludes patients with cancer diagnosed thereafter. Clearly, the longer these patients with myositis 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 antibody testing is not a foolproof method for detecting CAM, and development of a commercially viable test for anti-155/140 antibody is not on the horizon; therefore, physicians caring for patients with myositis must remain vigilant regarding cancer development with intensive yearly surveillance for 3–4 years after myositis onset.

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