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Defining cancer-risk, and assessing diagnostic usefulness of myositis serology, in dermatomyositis- Part 2

V Madan¹, H Chinoy², C E M Griffiths¹, and R G Cooper²

¹Dermatology, Salford Royal Hospital NHS Foundation Trust, The University of Manchester, Manchester, UK, M6 8HD

²Rheumatic Diseases Centres, Salford Royal Hospital NHS Foundation Trust, The University of Manchester, Manchester, UK, M6 8HD

Summary

In the first part of this review we examined the evidence behind the association between idiopathic inflammatory myopathies (IIM) and cancers. In view of the well-recognised association between cancer and myositis (hence the term cancer-associated myositis, or CAM) clinicians responsible for the management of patients with myositis must make important decisions regarding how intensively they undertake searches for malignancy. Clinicians must also decide how often such searches are repeated, and again how intensively, so as to optimise both cancer detection and treatment, and thus patient survival. As the risks of CAM are greatest in dermatomyositis, this is an issue of obvious importance to dermatologists. In this second of the two part review we examine the role of autoantibodies as potential predictors of cancer risk in IIM.

Keywords

Autoantibodies; cancer associated myositis; dermatomyositis; idiopathic inflammatory myopathies; malignancy; myositis; polymyositis

Several epidemiological studies have confirmed the association between cancer and myositis and that this risk is greatest in dermatomyositis (DM, see part 1). However, important clinical questions remain unanswered, e.g. the extent of investigations necessary to assess for the presence of malignancy at myositis onset, and thereafter. Reliable methods that would predict cancer risk in idiopathic inflammatory myopathies (IIMs) would clearly benefit patients and clinicians, yet such predictors have not been available until recently. Translation of epidemiological and laboratory research to the bedside in an attempt to predict cancer risk at myositis onset has led to encouraging results suggesting that myositis specific and myositis associated autoantibodies may reliably predict cancer risk in IIM.

Address for correspondence: V Madan, vishalmadan@doctors.org.uk.

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Cancer Screening Issues

Recommendations for cancer screening IIM patients have varied from careful history taking with clinical examination and routine laboratory screening, to much more invasive investigations.¹ Successful screening of IIM patients could allow for early identification of cancers, while successful anti-cancer therapies may result in better outcomes in cancer associated myositis (CAM).² In addition to careful history taking and examination, laboratory evaluation should include the following: full blood count, ESR, routine biochemistry, chest radiography, urinary cytology, faecal occult bloods, chest computed tomography (CT) scan, abdominal ultrasound/CT scan. In addition, mammography, pelvic ultrasound/CT scan, and gynaecological examination, appear justified in female patients.^{3,4}

Amoura *et al*⁵ assessed the diagnostic value of several circulating tumour markers for the detection of solid cancers in IIMs, and found that CA-125 and CA19-9 were useful in some patients, and so recommended that these should be used routinely in cancer searches, especially for those IIM patients without interstitial lung disease.⁵ However, other authors have not found tumour markers so useful.⁶ Most authors recommend age, sex and ethnically specific cancer screening. As an example, since colon cancer may be overrepresented in DM patients older than 65 years of age, lower gastrointestinal studies may be specifically indicated in this patient group.⁷ For PM patients, chest radiography and urinary cytology should be performed at the time of diagnosis targeting the commonest cancers in this cohort of patients, i.e. lung, bladder and non-Hodgkin lymphoma.⁸ Ovarian carcinoma is overrepresented in females with DM and may be difficult to detect.⁹ As cancer risk in DM remains high for 3, and possibly 5, years following DM diagnosis, continued surveillance is required.¹⁰ These recommendations are based on population-based cohort studies examining cancer risk in Caucasians.^{8, 11} When dealing with non-Caucasians IIM patients, such as South East Asians in whom the risk of nasopharyngeal carcinoma is clearly increased, cancer-type specific screening may be required.¹²⁻¹⁴ Increased cancer risk has been also reported in amyopathic DM,¹⁵ although population-based studies quantifying this risk are lacking. Until further epidemiological evidence is available, the same principles of malignancy screening should apply in this myositis subgroup. Given that accurate cancer searches may require potentially invasive screening procedures, which could need repeating, it is clear that reliable methods to predict those myositis patients most at risk of developing CAM would be of great benefit.

Diagnostic utility of myositis serology for predicting the likelihood of CAM

Tumour-associated autoimmunity can be directed to mutated forms of self-antigens (e.g. in melanoma), or to unrelated antigens associated with paraneoplastic syndromes.¹⁶ Examples of the latter include antibodies to the Yo/CDR2 antigen in paraneoplastic cerebellar degeneration in association with breast and ovarian cancers, and antibodies to Ri/NOVA (neuro-oncological ventral antigen) in paraneoplastic opsoclonus-myoclonus ataxia in patients with small cell lung, breast and ovarian cancers.¹⁷⁻¹⁹ Myositis-specific and myositis-associated autoantibodies (MSA, MAA) are present in about 40% of patients with myositis. These autoantibodies define subsets of IIM patients sharing similar clinical features, responses to therapy, immunogenetics and prognosis; thereby suggesting that they

may play specific immunopathogenic roles in myositis.²⁰ Antigens recognised by MAA include among others, PM-Scl, Ku, components of the U1 small nuclear RNP (snRNP) or the cytoplasmic Ro such as Ro60/SSA, La/SSB, and Ro52. Anti-synthetases are among the most frequent and most commonly tested for MSAs, of which the anti-histidyl tRNA synthetase (Jo-1) antibodies is the most common. Myositis patients with anti-Jo-1 antibodies (Abs) are prone to develop interstitial lung disease (ILD), Raynaud's phenomenon, arthropathy and 'mechanic's hands', a combination known as the anti-synthetase syndrome, but a negative association has been noted with this antibody and CAM.²⁰⁻²⁴ However, this negative association between malignancy and myositis occurring in the setting of anti-synthetase syndrome has been challenged in recent case reports.^{25,26}

Another relatively common MSA is the anti-Mi-2 Ab, which is detected almost exclusively in DM patients, and especially in those with typical cutaneous DM lesions and an absence of ILD.^{23,27} A recent, large study of Caucasian myositis patients found low anti-Mi-2 Ab frequencies in CAM,²⁸ however a European study suggested that cancer risk was increased, but only in anti-Mi-2 Ab positive patients possessing the N-terminal fragment of the Mi-2 antigen.²⁹ Anti-CADM140 Ab is associated with amyopathic DM and acute progressive interstitial pneumonia, but to date this Ab has not been linked with the development of malignancy.³⁰ In summary, many previous studies had attempted to identify serological markers associated with CAM, but until recently, serological profiles predictive of CAM had not emerged.^{1,2}

A new antibody has recently been reported other Abs were not detected, and may predict those myositis p in DM patients with or without CAM where atients most at risk of developing CAM. Anti-155/140 Ab was first described in both juvenile and adult DM patients by Targoff *et al*,³¹ occurring in 21% of non-CAM DM cases, in six of eight adult myositis patients with CAM and also in a relatively high proportion (75%) of juvenile DM patients (but without the presence of CAM).³² In a further small study Kaji *et al*³³ described anti-155/140 Ab in five of seven adult myositis patients with CAM. In both studies, none of the anti-155/140 Ab positive patients had interstitial lung disease, and so being consistent with the proposed negative association between ILD and cancer.¹⁰ The authors also noted cutaneous manifestations typical of DM in patients with the anti-155/140 antibody, and hypothesized that the 155/140 kDa antigen is highly expressed in cancers, skin and muscle, but not in lung, hence determining the phenotype.³⁴ While these results gave tantalising clues as to the potential aetiopathogenesis of DM and CAM, the patient numbers studied were too small to quantify the usefulness of the anti-155/140 Ab for CAM prediction.

To investigate further whether the risk of CAM is predictable by antibody profiling, Chinoy *et al*²⁴ studied a large cohort of Caucasian UK IIM adult cases. These patients were tested for a comprehensive range of MSA/MAAs. A summary of these serological findings is shown in Table 1. The results confirmed that anti-155/140 is DM-specific, being present in 19 of 103 DM patients, but in none of 109 with PM and none of the 70 with myositis overlapping with another connective tissue disease. Moreover, of the 16 CAM patients (defined according to the Bohan & Peter revised criteria³⁵) 15 were of the DM subtype, 8 of whom had the anti-155/140 Ab (Table 2). Testing for anti-155/140 antibody alone was 50% sensitive and 96% specific for detection of the CAM, with an excellent negative predictive

value. However, although the identity of the antigen target of anti-155/140 antibody is thought to be transcription intermediary factor 1- γ ,²⁴ it will be some time before a commercial kit for routine testing for this antibody is available. Chinoy *et al*²⁴ therefore used their results to evaluate the usefulness of routinely tested for myositis antibodies in a hospital laboratory setting (i.e. anti-Jo-1, -U1-RNP, -U3-RNP, -Ku and -PM-Scl) to predict CAM. As in previous studies, they found a paucity of “routine” antibodies in CAM patients, quantified as a 6-7 fold increased relative cancer risk in individuals lacking “routine antibodies” to those possessing such antibodies. They also confirmed that anti-Jo-1 antibodies and CAM, and ILD and CAM, both appear mutually exclusive. When combining the two strategies, i.e. no routinely detected antibodies and being anti-155/140 negative provided a 94% sensitivity and 99% negative predictive value, indicating that only 1% of patients with a routinely detected antibody or a negative anti-155/140 antibody had CAM. Moreover, when the DM patients were analysed alone, this strategy yielded 100% sensitivity and a 100% negative predictive value.²⁴ It was not significant for either observation, but CAM patients were also more likely to be males and of older age at onset of myositis. Figure 1 shows a suggested strategy for cancer search based on these latter results. Anti-Jo-1 Ab and ILD both are associated with a specific HLA class II haplotype,²⁴ and anti-155/140 Ab is associated with HLA-DQA1*0301,³² suggesting that cancer risk in IIMs may, at least in part, genetically determined.

Conclusions

The suggestion that having anti-Jo-1/ILD is protective of CAM appears to have been confirmed; in fact having any routine antibody appears protective, except where an individual patient with a routine antibody may also have an anti-155/140 antibody. Previous suggestions that being antibody -negative on routine testing increases the risk of CAM have now been confirmed and quantified i.e. conferring CAM-risk which is increased 6 -fold. However, this data is based on select cohorts and one must be aware in clinical practice that the presence of MSA/MAAs such as Jo-1 does not always indicate that CAM will never be found.^{25,26} The availability of a comprehensive MSA test panel incorporating the anti-155/140 Ab would obviously enhance the prediction of internal malignancy in these patients, and also guide cancer search intensities. However, until such facilities become routinely available, a negative routine myositis antibody screen, combined with the clinical features shown in Table 2 (part 1), should trigger a comprehensive cancer screen in myositis patients and especially those over the age of 50 years with DM.

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Figure1. Possible strategy for cancer search in cancer associated myositis (CAM) patients

Table 1Serological frequencies in myositis subgroups (from Chinoy *et al*²⁴)

	Polymyositis (n=105)	Dermatomyositis (n=103)	Myositis/CTD overlap (n=72)
Autoantibody status	n(%)	n(%)	n(%)
Myositis-specific auto-antibodies: *			
Jo-1	25 (23.8)	23 (22.3)	9 (12.5)
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 (4.8)	2 (1.9)	0
155/140	0	19 (18.4)	0
Myositis-associated auto-antibodies:			
U1-RNP	5 (4.8)	10 (9.7)	19 (26.4)
U3-RNP	0	2 (1.9)	2 (2.8)
Ku	0	2 (1.9)	3 (4.2)
PM-Scl	5 (4.8)	5 (4.8)	19 (26.4)
None of the above auto-antibodies			
	61 (58.1)	30 (29.1)	21 (29.2)

SRP=signal recognition particle; CTD=connective tissue disease

* PL-7, PL-12, EJ, OJ, KS are all anti-synthetases, like Jo-1

Table 2Serological frequencies in non-CAM and CAM patients (from Chinoy *et al* ²⁴)

	Non-CAM n (%)	CAM n (%)
Autoantibody status	(n=264)	(n=16)
Myositis-specific antibodies		
Jo-1	57 (21.6)	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 (6.1)	2 (12.5)
SRP	7 (2.7)	0
155/140	11 (4.2)	8 (50.0)
Myositis-associated antibodies		
U1-RNP	32 (12.1)	1 (6.2) *
U3-RNP	4 (1.5)	0
Ku	5 (1.9)	0
PM-Scl	29 (11.0)	0
None of the above auto-antibodies		
	106 (40.2)	6 (37.5)

CAM=cancer associated myositis

Numbers do not add up to totals due to presence of patients with multiple -Abs

Risk of CAM: anti-155/140 Ab positive vs. anti-155/140 Ab negative, $p=0.0009$, odds ratio 23.0, 95% confidence interval 6.1-83.8

* The two CAM patients with anti KS and anti U1-RNP Abs also had anti 155/140 Abs.