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RESEARCH ARTICLE

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Analysis of myositis autoantibodies in Chinese patients with cancer-associated myositis

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Abstract

Background: Cancer-associated myositis (CAM) has poor prognosis and causes higher mortality. In general, myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) have been shown to be useful biomarkers for its diagnosis.

Methods: In the present study, focus was given in assessing the presence, prevalence, and diagnostic values of myositis autoantibodies in Chinese patients diagnosed with CAM. The sera collected from 49 CAM patients, 108 dermatomyositis/polymyositis (DM/PM) patients without cancer, 105 disease controls, and 60 healthy controls were detected for the presence of 16 autoantigens (Jo-1, OJ, EJ, PL-7, PL-12, MDA5, TIF1γ, Mi-2α, Mi-2β, SAE1, NXP2, SRP, Ku, PM-Scl75, PM-Scl100, and Ro-52) using a commercial Euroline assay.

Results: The frequency of anti-TIF1γ was significantly higher in CAM patients than in DM/PM patients without cancer (46.9% vs 14.8%, $P < .001$). Importantly, the sensitivity and specificity for this MSA were 46.9% and 85.2%, respectively. These helped to differentiate CAM patients from DM/PM patients without cancer. However, there was no difference in other MSAs and MAAs between CAM and DM/PM patients without cancer.

Conclusion: The present study indicates that anti-TIF1γ levels can serve as important biomarkers for CAM diagnosis and help in distinguishing between CAM and DM/PM patients without cancer.

KEYWORDS

cancer-associated myositis, myositis-associated autoantibodies, myositis-specific autoantibodies

1 | INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are usually characterized by proximal muscle weakness and are a heterogeneous group of disorders, which includes dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), juvenile idiopathic myositis (JIM), and sporadic inclusion body myositis (sIBM).[1] The association of cancer with IIMs has been known for a long time,

especially in DM and PM patients, and has been defined as cancer-associated myositis (CAM).[2-4] In 1916, Stertz was the first to report the association between cancer and DM.[5] Since then, multiple additional studies have described the association between cancer and DM/PM and reported that its global cancer rate ranged within 11.2%-21.0%.[6-10] Furthermore, some studies have demonstrated that DM patients have a greater risk of cancer than PM patients.[7] The standardized incident ratio (SIR) for developing cancer ranges within 2.2-6.5 in DM, while this varies within 1.7-2.2 in PM patients.[2] The overall prognoses of CAM patients have been poor and generally displayed an increased risk of mortality.[6,11,12] Thus, early detection and appropriate treatment are important for managing patients with CAM.

Importantly, electromyography, muscle biopsy, and muscle enzyme levels have been the standard diagnostic and classification criteria for IIMs. In addition, myositis autoantibodies have also been suggested to be important biomarkers in IIM diagnosis and classification and are typically categorized as myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs).[13] Among these autoantibodies, MSAs are specific to IIMs, while MAAs are mostly observed in myositis-overlap syndrome and other connective tissue diseases (CTDs). However, the corresponding target autoantigens of both MSAs and MAAs are involved in protein synthesis and translocation, gene transcription, viral recognition, and innate immunity.[14,15] Various studies have demonstrated that MSAs and MAAs both serve as useful diagnostic and prognostic biomarkers in CAM patients.[16-21]

In the present study, the investigators attempted to determine the frequency and diagnostic potential of MSAs (anti-Jo-1, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-MDA5, anti-TIF1γ, anti-Mi-2α, anti-Mi-2β, anti-SAE1, anti-NXP2, and anti-SRP) and MAAs (anti-Ku, anti-PM-Scl75, anti-PM-Scl100 anti-Ro-52), specifically in Chinese patients with CAM, and investigated the individual diagnostic values in distinguishing CAM patients from DM/PM patients without cancer.

2 | MATERIAL AND METHODS

2.1 | Patients

In the present study, a total of 157 adult DM/PM patients were analyzed. Among these patients, 49 patients were diagnosed with CAM, while the remaining 108 DM/PM patients were diagnosed without cancer. The DM and PM diagnoses were based on the Bohan and Peter criteria.[22,23] CAM is defined as cancer that occurs within 3 years (before or after) of the DM/PM diagnosis.[20,24] In addition, 60 healthy subjects and 105 patients with other CTDs, which included 25 patients with pSS,[25] 25 patients with RA,[26] 25 patients with SLE[27] and 30 patients with SSc,[28] were included in the present analysis. These participants were assigned as healthy and disease controls, respectively. Serum samples and informed consent forms were obtained from each subject. The present study was approved by the Ethics Committee of Peking Union Medical College Hospital, Beijing, China.

2.2 | Assay for myositis autoantibodies

A total of 322 serum samples were analyzed for various myositis autoantibodies using a commercial line blot assay (EUROLINE Autoimmune Inflammatory Myopathies 16 Ag [IgG] Euroimmun), according to manufacturer's instructions. Each strip of the assay included the following autoantigens: Jo-1, OJ, EJ, PL-7, PL-12, MDA5, TIF1γ, Mi-2α, Mi-2β, SAE1, NXP2, SRP, Ku, PM-Scl75, PM-Scl100, and Ro-52. Finally, the signal for each autoantibody from the individual assay strip was interpreted using a scanning software (Euroimmun) and categorized as negative, borderline, or positive.

2.3 | Statistical analysis

All data were statistically analyzed using the SPSS 20.0 (IBM Corporation) software. Categorical variables were compared using chi-square or Fisher's exact test. A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The demographic and clinical features of the enrolled subjects are summarized in Table 1. Forty-nine CAM patients and 108 DM/PM patients without cancer were included. The control groups comprised of 105 patients as disease controls and 60 healthy subjects as healthy controls.

3.2 | The association between cancer type and myositis-specific autoantibodies

Thirty-seven CAM patients were observed to be positive for one MSA. The distribution of MSAs in different cancers is listed in Table S1. Anti-TIF1γ autoantibody was the most prevalent in patients with CAM. Twenty-three of 49 CAM patients were positive for anti-TIF1γ autoantibody.

3.3 | Comparison of myositis autoantibody prevalence in CAM patients, DM/PM patients without cancer, disease controls, and healthy subjects

The overall prevalence of myositis autoantibodies between the different patient groups and controls is summarized in Table 2. Specifically, the prevalence of anti-PL-7, anti-MDA5, anti-Ku,

TABLE 1 The characteristics of cancer-associated myositis patients and dermatomyositis/polymyositis patients without cancer

	CAM	DM/PM without cancer	DC	HC
Total	49	108	105	60
Mean age ± SD	56.39 ± 10.83	45.47 ± 14.51	46.09 ± 15.18	45.36 ± 12.38
Male/female	14/35	29/79	32/73	20/40
DM/PM	41/8	81/27	—	—
Breast cancer	9 (18.4%)	—	—	—
Ovarian cancer	9 (18.4%)	—	—	—
Lung cancer	8 (16.3%)	—	—	—
Nasopharynx cancer	5 (10.2%)	—	—	—
Thyroid cancer	5 (10.2%)	—	—	—
Colon cancer	4 (8.2%)	—	—	—
Gastric cancer	3 (6.1%)	—	—	—
Cervical cancer	1 (2.0%)	—	—	—
Endometrial cancer	1 (2.0%)	—	—	—
Liver cancer	1 (2.0%)	—	—	—
Bladder cancer	1 (2.0%)	—	—	—
Synovial sarcoma	1 (2.0%)	—	—	—
Breast cancer + endometrial cancer	1 (2.0%)	—	—	—

Abbrevaitions: CAM, cancer-associated myositis; DC, diseases controls; DM/PM, dermatomyositis/polymyositis; HC, healthy controls; SD, standard deviation.

anti-PM-Scl75, anti-PM-Scl100, and anti-Ro-52 autoantibodies in disease controls was 1.9%, 1.9%, 3.8%, 3.8%, 1.9%, and 40.0%, respectively. In addition, 96.2% of the disease controls were negative for any MSA. Importantly, none of the healthy subjects were positive for MSA. However, anti-PM-Scl75 and anti-Ro-52 MAA levels were indeed detected in 1.7% and 3.3% of healthy controls, respectively. Moreover, no significant differences were observed in anti-Jo-1, anti-EJ, anti-PL-7, anti-PL-12, anti-MDA5, anti-Mi-2α, anti-Mi-2β, anti-SAE1, anti-NXP2, anti-SRP, anti-Ku, anti-PM-Scl75, anti-PM-Scl100, anti-Ro-52, and MSAs negative between CAM and DM/PM patients without cancer (all, $P > .05$). The prevalence of anti-TIF1γ was observed to be significantly higher in CAM patients, when compared to DM/PM patients without cancer (46.9% vs 14.8%, $P < .001$).

3.4 | Predictive power analysis of myositis autoantibodies to distinguish CAM and DM/PM patients without cancer

In identifying the potential of these analyzed myositis autoantibodies in distinguishing CAM patients from DM/PM patients without cancer, it was observed that anti-TIF1γ has the highest sensitivity, followed by anti-Ro-52 and MSAs negative (Table 3). The sensitivities of anti-Jo-1, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-MDA5, anti-Mi-2α, anti-Mi-2β, anti-SAE1, anti-NXP2, anti-SRP, anti-Ku, anti-PM-Scl75, and anti-PM-Scl100 autoantibodies were all < 10%. Importantly, the specificities of anti-Jo-1, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-Mi-2α, anti-Mi-2β, anti-SAE1, anti-NXP2, anti-SRP, anti-Ku, anti-PM-Scl75, and anti-PM-Scl100 autoantibodies in distinguishing both patient groups were >90%, while anti-MDA5, anti-TIF1γ, anti-Ro-52, and MSAs negative had relatively lower specificities.

4 | DISCUSSION

Although cancer has been one of the IIM-related causes of death[6,29] and CAM patients have an increased risk of mortality,[11,30] the pathogenesis of developing cancer in myositis patients remains poorly understood. Typically, CAM has been proposed to be caused by altered cellular and humoral immunity, in which immune response directed against cancer can cross-react with regenerating muscle cells.[31] This indicates that autoantibodies can serve as a useful tool in evaluating CAM patients. In the present study, 49 CAM patients, 108 DM/PM patients without cancer, 105 disease controls, and 60 healthy controls were enrolled to explore the presence, prevalence, and diagnostic potential of myositis autoantibodies. The present analysis mainly indicated that most CAM patients were positive for one MSA. However, some of these were also negative for MSAs. The prevalence of anti-TIF1γ autoantibody was significantly higher in CAM patients, when compared to DM/PM patients without cancer. In addition, anti-TIF1γ autoantibody exhibited higher sensitivity and specificity in differentiating CAM patients from DM/PM patients without cancer.

TABLE 2 The prevalence of myositis autoantibodies in patients with cancer-associated myositis, dermatomyositis/polymyositis patients without cancer, disease controls, and healthy controls

	CAM		DM/PM without cancer		DC		HC		*P*-value CAM vs DM/PM without cancer
Number of subjects	49	%	108	%	105	%	60	%	
MSAs positive									
Anti-Jo-1	4	8.2	9	8.3	0	0.0	0	0.0	1.000
Anti-OJ	0	0.0	0	0.0	0	0.0	0	0.0	NA
Anti-EJ	0	0.0	1	0.9	0	0.0	0	0.0	1.000
Anti-PL-7	3	6.1	1	0.9	2	1.9	0	0.0	.171
Anti-PL-12	1	2.0	2	1.9	0	0.0	0	0.0	1.000
Anti-MDA5	2	4.1	15	13.9	2	1.9	0	0.0	.067
Anti-TIF1γ	23	46.9	16	14.8	0	0.0	0	0.0	<.001
Anti-Mi-2α	1	2.0	5	4.6	0	0.0	0	0.0	.738
Anti-Mi-2β	0	0.0	5	4.6	0	0.0	0	0.0	.298
Anti-SAE1	1	2.0	3	2.8	0	0.0	0	0.0	1.000
Anti-NXP2	1	2.0	7	6.5	0	0.0	0	0.0	.435
Anti-SRP	1	2.0	2	1.9	0	0.0	0	0.0	1.000
MAAs positive									
Anti-Ku	2	4.1	6	5.6	4	3.8	0	0.0	1.000
Anti-PM-Scl75	2	4.1	3	2.8	4	3.8	1	1.7	1.000
Anti-PM-Scl100	0	0.0	1	0.9	2	1.9	0	0.0	1.000
Anti-Ro-52	19	38.8	34	31.5	42	40.0	2	3.3	.371
Negative									
MSAs negative	12	24.5	42	38.9	101	96.2	60	100.0	.078

Abbreviations: CAM, cancer-associated myositis; DC, diseases controls; DM/PM, dermatomyositis/polymyositis; HC, healthy controls; MAAs, myositis-associated autoantibodies; MSAs, myositis-specific autoantibodies.

Due to the small number of cases examined, the results in the present study should be interpreted with caution, and additional studies with a larger sample size are needed to verify these results.

Anti-TIF1γ autoantibody is usually regarded as a key biomarker in the prediction and diagnosis of CAM.[7,19] Malignancy is more common in patients with anti-TIF1γ autoantibody than in patients without anti-TIF1γ autoantibody.[32,33] In Asia, approximately 50% of adult patients with CAM were positive for anti-TIF1γ autoantibody.[6,33,34] Seven of 12 (58.3%) Japanese patients with CAM described by Hoshino et al[33] and 23 of 41 (56.1%) adult Japanese DM patients with cancer reported by Ogawa-Momohara et al[34] were positive for anti-TIF1γ autoantibody. In addition, Yang et al found that 34 of 89 anti-TIF1γ-positive patients with IIMs had cancer.[6] In the present study, the frequency of anti-TIF1γ autoantibody in CAM (46.9%) was in accordance with that found in previous studies.[6,33,34] An earlier study exhibited that anti-TIF1γ is associated with CAM, which has a sensitivity of 55.6% and a specificity of 89.7%.[18] In the present study, it was also noticed that anti-TIF1γ was the most common autoantibody in CAM patients, which has a relatively low sensitivity (46.9%) and specificity (85.2%) for distinguishing CAM patients from DM/PM patients without cancer.

Anti-TIF1γ autoantibody was originally described as anti-p155 autoantibody directed against a 155-kDa nuclear protein.[35] Specifically, the TIF1γ antigen is a member of the TIF1 family of proteins that belongs to the tripartite motif (TRIM) superfamily.[36] It functions as a tumor suppressor protein by preventing the degradation of nuclear β-catenin,[37] and a regulator of epithelial-mesenchymal transition[38,39] and chromatin.[40] Its tumor suppressor role has been highlighted in multiple cancers, including myelomonocytic leukemia,[41] pancreatic cancer,[42,43] hepatocellular carcinoma,[44] and non-small-cell lung cancer.[45] In contrast, TIF1γ has also been observed to be overexpressed in the early stages of colorectal carcinogenesis.[46] Therefore, all these studies indicate the strong association between TIF1γ expression and cancer. However, its actual contribution to cancer pathogenesis remains elusive.

Previous studies have also reported the association of anti-NXP2 autoantibody with CAM.[47] However, the present analysis revealed no difference in anti-NXP2 levels between CAM and DM/PM patients without cancer. This contradiction can be attributed to the different ethnic backgrounds of Chinese patients or the small sample size of patients with CAM. Thus, well-designed prospective studies with a large sample size would be helpful in fully understanding the association between CAM and anti-NXP2 autoantibody.

TABLE 3 The predictive power of myositis autoantibodies in differentiating cancer-associated myositis patients from dermatomyositis/polymyositis patients without cancer

CAM vs DM/PM without cancer	SEN	SPE	PPV	NPV	LR+ (95% CI)	LR- (95% CI)
MSAs positive						
Anti-Jo-1	8.2%	91.7%	30.8%	68.8%	1.0 (0.32-3.03)	1.0 (0.91-1.11)
Anti-OJ	0.0%	100.0%	NA	68.8%	NA	1.0 (1.00-1.00)
Anti-EJ	0.0%	99.1%	0.0%	68.6%	0.0	1.0 (0.99-1.03)
Anti-PL-7	6.1%	99.1%	75.0%	69.9%	6.6 (0.71-61.98)	0.9 (0.88-1.02)
Anti-PL-12	2.0%	98.2%	33.3%	68.8%	1.1 (0.10-11.87)	1.0 (0.95-1.05)
Anti-MDA5	4.1%	86.1%	11.8%	66.4%	0.3 (0.07-1.24)	1.1 (1.01-1.23)
Anti-TIF1γ	46.9%	85.2%	59.0%	78.0%	3.2 (1.84-5.45)	0.6 (0.47-0.82)
Anti-Mi-2α	2.0%	95.4%	16.7%	68.2%	0.4 (0.05-3.67)	1.0 (0.97-1.09)
Anti-Mi-2β	0.0%	95.4%	0.0%	67.8%	0.0	1.05 (1.01-1.09)
Anti-SAE1	2.0%	97.2%	25.0%	68.6%	0.7 (0.08-6.89)	1.0 (0.96-1.06)
Anti-NXP2	2.0%	93.5%	12.5%	67.8%	0.3 (0.04-2.49)	1.0 (0.98-1.12)
Anti-SRP	2.0%	98.2%	33.3%	68.8%	1.1 (0.10-11.87)	1.0 (0.95-1.05)
MAAs positive						
Anti-Ku	4.1%	94.4%	25.0%	68.5%	0.7 (0.15-3.51)	1.0 (0.94-1.09)
Anti-PM-Scl75	4.1%	97.2%	40.0%	69.1%	1.5 (0.25-8.52)	1.0 (0.92-1.05)
Anti-PM-Scl100	0.0%	99.1%	0.0%	68.6%	0.0	1.0 (0.99-1.03)
Anti-Ro-52	38.8%	68.5%	35.9%	71.2%	1.2 (0.79-1.93)	0.9 (0.69-1.16)
Negative						
MSAs negative	24.5%	61.1%	22.2%	64.1%	0.6 (0.37-1.09)	1.2 (0.99-1.54)

Abbreviations: CAM, cancer-associated myositis; CI, confidence interval; DM/PM, dermatomyositis/polymyositis; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NA, not available; NPV, negative predictive value; PPV, positive predictive value; SEN, sensitivity; SPE, specificity.

In conclusion, the present analysis demonstrated that most of the CAM patients were positive for MSAs and that anti-TIF1γ autoantibody can be helpful in diagnosing CAM patients and serve as a biomarker to distinguish these patients from DM/PM patients without cancer.

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CONFLICT OF INTEREST

The authors declare that they have no competing financial interests.

AUTHOR CONTRIBUTIONS

LLB and LCX designed the study, conducted all the searches, appraised all potential studies, and wrote and revised the draft manuscript and subsequent manuscripts. WQ, WCY, ZFF, CLL, WXT, and ZXF assisted in collecting sera. ZFC and LYZ conceived and designed the study, assisted with the searches, appraised relevant studies and assisted in drafting and revising the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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