Increased Levels of Soluble Programmed Death Ligand 1 Associate with Malignancy in Patients with Dermatomyositis

He Chen, Qinglin Peng, Hanbo Yang, Liguo Yin, Jingli Shi, Yamei Zhang, and Guochun Wang

ABSTRACT. ***Objective.*** To investigate the levels of soluble programmed death ligand 1 (sPD-L1) and evaluate its association with malignancy in patients with dermatomyositis (DM).

Methods. Levels of sPD-L1 were measured in serum from 88 DM patients without malignancies (sDM), 40 with cancer-related DM (CRDM), and 30 healthy controls (HC) using ELISA. The CRDM subjects were divided into new-onset cancers (nCRDM) and stable cancers (sCRDM). Receiver-operating characteristic (ROC) curve analysis was performed to determine the cutoff sPD-L1 value that distinguished patients with nCRDM from those who were sDM. Serum antitranscriptional intermediary factor 1-γ (TIF1-γ) antibodies were detected using immunoblot, and the diagnostic values for malignancy were compared with sPD-L1 levels in patients with DM.

Results. Serum sPD-L1 levels were significantly higher in sDM [median 12.3 ng/ml, interquartile range (IQR) 8.4–16.2] than in HC (median 1.3 ng/ml, IQR 0.4-2.2, p = 0.0001). Extremely high sPD-L1 levels were seen in nCRDM (median 18.5 ng/ml, IQR 13.8–22.4), much higher than those in sCRDM (median 8.5 ng/ml, IQR 6.8–11.8, p = 0.0001). The sPD-L1 levels in 4 patients with nCRDM decreased after curative cancer treatment (p = 0.013). ROC curve analysis revealed that the sPD-L1 value distinguishing nCRDM from sDM was 16.1 ng/ml, with an area under the curve value of 0.72 ± 0.04 (p = 0.0001). The combination of sPD-L1 and anti-TIF1-γ antibodies yielded greater specificity and positive predictive value in diagnosing cancer, reaching values of 95% and 70%, respectively.

Conclusion. Serum sPD-L1 levels increased significantly in sDM, and markedly high sPD-L1 levels could be a diagnostic indicator for malignancies in patients with DM, especially in those with anti-TIF1-γ antibodies. (First Release February 1 2018; J Rheumatol 2018;45:835–40; doi:10.3899/jrheum.170544)

Key Indexing Terms:
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Dermatomyositis (DM) is a group of heterogeneous, systemic autoimmune disorders that are characterized by muscle weakness and rashes[1]. The incidence of DM is rare and the pathogenesis underlying DM is both complicated and still unclear. One remarkable characteristic of patients with DM is their tendency to develop cancer[2,3]. A population-based study from Taiwan showed that during the first 3 to 5 years after the onset of DM in Chinese adults, the standardized incidence ratios for developing malignancy was 5:11[4]. The types of malignancies vary and include hematologic malignancies as well as solid cancers such as ovarian, breast, colon, and nasopharyngeal cancer[5,6].

The programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway, a member of the inhibitory B7 family, functions to limit, attenuate, or even terminate T cell responses, thus preventing T cell hyperactivation and inducing immune tolerance[7,8]. As a consequence, the PD-1/PD-L1 pathway plays a key role in autoimmunity and antitumor immunity[9,10]. Some studies have reported high levels of PD-L1 expression in human tumors and tumors can at times stimulate PD-L1 expression to silence the immune system[9,11,12].

Some advances have been made in recent years to define specific features of cancer-related DM (CRDM). One of these features is the presence of myositis-specific antibodies

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(MSA), which contribute to classify distinct phenotypes and categorize patients into more homogeneous subgroups[13]. Patients with MSA recognizing either antitranscriptional intermediary factor 1γ (anti-TIF1-γ) or antinuclear matrix protein 2 have been reported to face higher risks for malignancy[14,15,16]. However, no other specific serological markers predict the onset of malignancy precisely in patients with DM. Because several studies performed in cancer patients indicated that soluble programmed death ligand 1 (sPD-L1) expression was elevated in sera and was associated with poor prognosis[17,18,19], we studied whether sPD-L1 concentrations could be a serological marker for the presence of malignancies in patients with DM. Here we aimed to investigate the expression of sPD-L1 and to evaluate its association with malignancy in patients with DM.

MATERIALS AND METHODS

Patients. A total of 128 Han Chinese patients who fulfilled the Bohan and Peter criteria[20] for classic DM or the Sontheimer criteria for clinically amyopathic DM[21,22] were enrolled in our study. Among these patients, 40 were identified as CRDM, and the remaining 88 patients without malignancies were classified as standard DM (sDM) patients. Based on the most commonly used criteria, CRDM was defined as the onset of cancer within 3 years of the DM diagnosis[15,23]. The CRDM cohort consisted of these cancers: breast (8 patients), ovarian (6), lung (6), nasopharyngeal (4), thyroid (3), cervical (2), esophageal (2), colorectal (2), hepatic (1), gastric (1), thymic (1), mediastinal (1), and lymphomas (3). The CRDM subjects were divided into 2 groups: patients with new-onset cancers (n = 22; nCRDM) and patients with stable cancers (n = 18; sCRDM). New-onset cancers were defined as those that were diagnosed within half a year of the DM diagnosis, and the patients had not received any treatment for cancer. Stable cancers were defined as cancers that had been treated with curative surgery and/or standard chemotherapy and were in remission. Then 4 patients with nCRDM who underwent curative treatment for cancer were followed and the changes in their sPD-L1 concentrations before and after treatment were assessed. Patients' characteristics, including demographic features, clinical features, and laboratory data were collected from electronic medical records at the time of blood sampling.

The control groups included 78 disease controls [24 with rheumatoid arthritis (RA), 24 with systemic lupus erythematosus (SLE), and 30 with solid cancers] and 30 healthy controls (HC). The sera of 30 patients with pretreated solid cancers were obtained from the Department of Thoracic Surgery of the China-Japan Friendship Hospital and the types of cancer included lung, esophageal, and mediastinal cancers. HC were selected from the Department of Health Examination of the China-Japan Friendship Hospital and were age- and sex-matched to the sDM cohort.

Our study was approved by the Research Review Committee and the Ethical Review Committee of the China-Japan Friendship Hospital (registration no. 2016-117).

Measurement of serum sPD-L1 concentrations and detection of anti-TIF1-γ antibodies (Abs). All blood samples collected by venipuncture clotted for 30 min at room temperature and then the serum samples were separated by centrifuging at 2500 rpm for 10 min. Then the serum was distributed in sterile tubes and stored at –80°C until the analysis. The total time between blood draw and freezing at –80°C would not exceed 1 h. Serum sPD-L1 levels were measured using an ELISA (PDCD1LG1 ELISA kit, USCN Life Science) according to the manufacturer's protocol. Each sample was tested in duplicate. Serum anti-TIF1-γ Abs were detected using EUROIMMUN Immunoblot according to the manufacturer's instructions.

Statistical analysis. All data are presented as absolute values and percentages, means ± SD, or medians and interquartile range (IQR). For continuous variables, data were compared using the independent t test for 2 independent samples and the Mann-Whitney U test for non-normal distributed samples. The differences in sPD-L1 levels before and after curative cancer treatment in 4 patients with nCRDM were tested by using the paired t test. The values of sPD-L1 levels in different groups were transformed into normal-distributed data by base-10 logarithm transformation and were adjusted for confounders by ANCOVA. For categorical variables, data were compared using the chi-square test. Receiver-operating characteristic (ROC) curve analysis was performed and the point with maximum Youden Index was selected as the cutoff value. Statistical analyses were carried out using SPSS software (version 21.0), and the ROC curve was drawn using MedCalc (version 17.2). The figures were plotted by using GraphPad Prism 5 (version 5.01). P values (2-sided) < 0.05 were considered statistically significant.

RESULTS

Patient characteristics. Eighty-eight sDM patients and 40 patients with CRDM were enrolled in our study and their demographic, clinical, and laboratory features are listed in Table 1. Compared with sDM, patients with CRDM presented with older age, shorter disease duration, a greater percentage with muscle weakness and dysphagia, and a higher rate of carrying the anti-TIF1-γ Abs.

Increased serum sPD-L1 concentrations found in sDM patients. Compared to HC (median 1.3 ng/ml, IQR 0.4–2.2), the serum sPD-L1 concentrations were significantly higher in sDM patients (median 12.3 ng/ml, IQR 8.4–16.2, p = 0.0001). Interestingly, serum sPD-L1 concentrations were also higher in patients with SLE and RA. Median sPD-L1 levels were 9.0 ng/ml (IQR 6.7–12.5) in SLE and 12.8 ng/ml (IQR 10.3–19.5) in RA (Figure 1).

Serum sPD-L1 concentrations associated with malignancy in CRDM patients. To investigate the association between serum sPD-L1 expression and malignancy, sPD-L1 concentrations were measured in 40 CRDM patients and 30 patients with solid cancers. As shown in Figure 2A, patients with solid cancers had the highest sPD-L1 levels (median 27.6 ng/ml, IQR 20.6–31.8), while nCRDM had higher serum sPD-L1 levels (median 18.5 ng/ml, IQR 13.8–22.4) than did sDM patients (median 12.3 ng/ml, IQR 8.4–16.2, p = 0.003). To determine whether the stage of cancer would affect sPD-L1 levels, nCRDM was compared with sCRDM, and the sPD-L1 levels in nCRDM were much higher than those in patients with sCRDM (median 8.5 ng/ml, IQR 6.8–11.8, p = 0.0001). For further validation, 4 patients with nCRDM received followup and their sPD-L1 levels were measured before and after they underwent cancer treatments. As shown in Figure 2B, sPD-L1 levels decreased after curative treatment (mean before treatment 20.9 ± 7.9 ng/ml vs after treatment 12.1 ± 7.3 ng/ml, p = 0.013).

It has been reported that sPD-L1 expressed in normal human serum and the concentration increased in an age-dependent manner[24]. In addition to age, sPD-L1 levels may also be influenced by disease duration and immunosuppressive agents using history. After adjustment for age, ANCOVA indicated that patients with solid cancers still had

Table 1. Demographic, clinical, and laboratory features of sDM patients, CRDM patients, and control groups.

	sDM, n = 88	CRDM, n = 40	SLE, n = 24	RA, n = 24	Solid Cancers, n = 30	HC, n = 30	p[b]
				Control Groups[a]			
Demographic features							
Female (%)	63 (71.6)	25 (62.5)	19 (79.2)	17 (70.8)	14 (46.7)	21 (70)	0.146
Age, yrs, mean ± SD	49.8 ± 13.2	57.4 ± 12.1	32.9 ± 11.4	52.5 ± 14.3	60.8 ± 10.9	47.9 ± 10.1	0.002
Ethnicity	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	—
Disease duration, mos, median and IQR	8.5 (0.3–216)	4 (0.3–168)	9.2 (0.5–128)	13.1 (2–282)	4.3 (0.6–9.5)	—	0.023
Clinical features, n (%)							
Muscle weakness	48 (54.5)	31 (77.5)					0.04
Interstitial lung disease	41 (46.5)	14 (35)					0.092
Dysphagia	14 (15.9)	23 (57.5)					0.0001
Laboratory features							
Muscle biopsy, n (%)	61 (69.3)	19 (47.5)					—
Median CK at enrollment (range)	84 (23–17,721)	233 (14–9505)					0.074
MSA, n (%)	64 (72.7)	35 (87.5)					0.096
Antisynthetase[c]	15 (23.4)	3 (8.5)					0.178
Anti-TIF1-γ	12 (18.7)	28 (80)					0.0001
Anti-NXP-2	7 (10.9)	1 (2.8)					0.110
Anti-Mi-2	10 (15.6)	1 (2.8)					1.000
Anti-SRP	1 (1.5)	0					—
Anti-HMGCR	2 (3.1)	1 (2.8)					1.000
Anti-MDA5	15 (23.4)	0					—
Anti-SAE	2 (3.1)	2 (5.6)					0.589

[a] Control groups include disease controls (SLE, RA, solid cancers) and HC. [b] p value between sDM and CRDM patients. [c] Common antisynthetase antibodies include anti-Jo1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS. CK: creatine kinase; DM: dermatomyositis; sDM: DM without malignancies; CRDM: cancer-related DM; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HC: healthy controls; IQR: interquartile range; MSA: myositis-specific antibodies; anti-TIF1-γ: antitranscriptional intermediary factor 1γ; NXP-2: antinuclear matrix protein 2; SRP: signal recognition particle; HMGCR: 3-hydroxy-3-methyl coenzyme A reductase protein; MDA5: melanoma differentiation-associated gene 5 protein; SAE: small ubiquitin-like modifier activating enzyme.
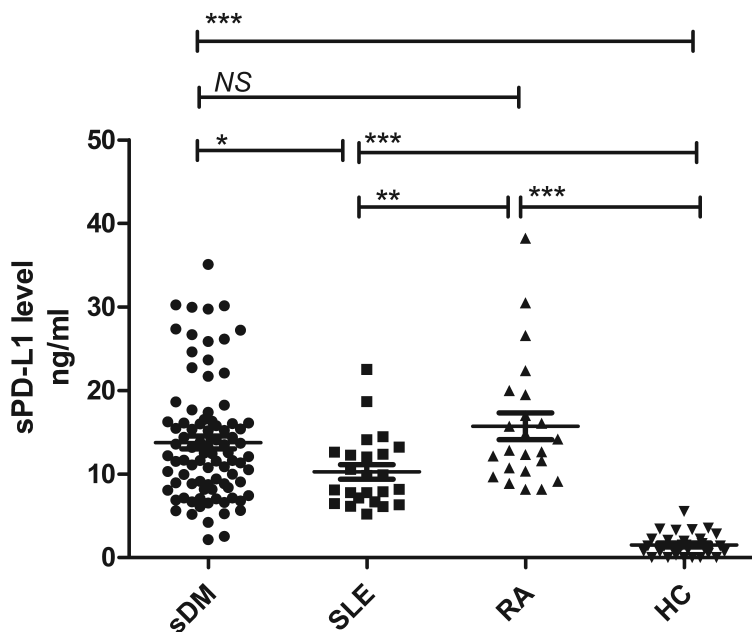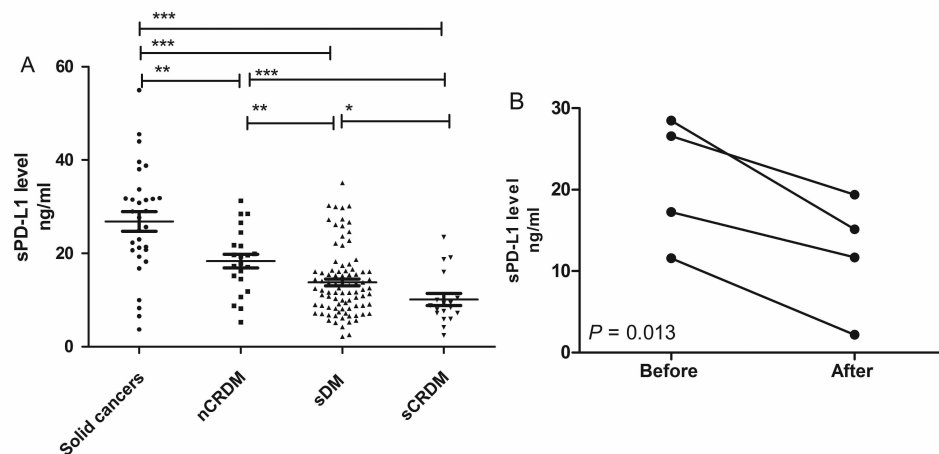

Figure 1. Serum sPD-L1 levels in patients with sDM, SLE, and RA, and in HC. Significantly higher serum levels of sPD-L1 were found in patients with sDM than in HC (p = 0.0001). The levels of sPD-L1 were also higher in patients with SLE and RA compared to those in HC. *p < 0.05, **p < 0.005, ***p < 0.0005. sPD-L1: soluble programmed death ligand 1; sDM: dermatomyositis without malignancies; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HC: healthy controls; NS: not significant.

Figure 2. Association between serum sPD-L1 levels and malignancy. A. The highest serum sPD-L1 levels were seen in patients with solid cancers, while much higher sPD-L1 levels were found in patients with nCRDM than in sDM patients and patients with sCRDM. B. sPD-L1 levels decreased after curative treatment for cancer in 4 patients with nCRDM (p = 0.013). *p < 0.05, **p < 0.005, ***p < 0.0005. sPD-L1: soluble programmed death ligand 1; DM: dermatomyositis; sDM: DM without malignancies; nCRDM: new-onset cancer-related DM; sCRDM: stable cancers with DM.

higher sPD-L1 levels than patients with nCRDM, sDM, and sCRDM (all p < 0.05). After adjustment for age, disease duration, and immunosuppressive agents using history between nCRDM, sDM, and sCRDM patients, sPD-L1 levels in nCRDM were still higher than those in sDM and sCRDM (all p < 0.03), which were in accord with our previous results. The mean serum sPD-L1 levels in different groups by ANCOVA are shown in Table 2.

Diagnostic value of sPD-L1 concentrations for patients with nCRDM. Because markedly high levels of sPD-L1 were found in patients with nCRDM, we hypothesized that sPD-L1 levels might have diagnostic value for the occurrence of cancers. To determine how sPD-L1 levels might differentiate between nCRDM and sDM, ROC curve analysis was

performed. As shown in Figure 3, the cutoff value of sPD-L1 levels that distinguished nCRDM patients from sDM patients was 16.1 ng/ml, with an area under curve value of 0.72 ± 0.04 (p = 0.0001). The sensitivity and specificity were 68% and 76%, respectively.

Because patients carrying the anti-TIF1-γ Abs have been reported to face higher risk of developing cancer, we considered whether the combination of sPD-L1 concentrations and anti-TIF1-γ Abs could diagnose the occurrence of cancer more precisely. Therefore, we compared sPD-L1 concentrations alone, and anti-TIF1-γ Abs alone with sPD-L1 concentrations and anti-TIF1-γ Abs together by considering 4 diagnostic values: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The

Table 2. The mean serum sPD-L1 levels in different groups[a] by ANCOVA.

	sDM	nCRDM	sCRDM	SLE	RA	Solid Cancers	HC
Model 1[b]							
Mean ± SD	1.080 ± 0.025	1.227 ± 0.041	0.945 ± 0.056	0.978 ± 0.165	1.156 ± 0.182	1.341 ± 0.052	0.187 ± 0.061
95% CI	1.030–1.130	1.141–1.313	0.825–1.064	0.908–1.049	1.077–1.235	1.234–1.447	0.060–0.314
Model 2[c]							
Mean ± SD	1.084 ± 0.026	1.208 ± 0.052	0.931 ± 0.058	0.956 ± 0.148	1.143 ± 0.183	1.337 ± 0.051	0.212 ± 0.053
95% CI	1.032–1.135	1.115–1.314	0.816–1.046	0.912–1.037	1.067–1.214	1.222–1.458	0.107–0.317
Model 3[d]							
Mean ± SD	1.086 ± 0.025	1.216 ± 0.050	0.932 ± 0.055				
95% CI	1.037–1.135	1.117–1.315	0.823–1.041				

[a] The values of serum sPD-L1 levels underwent base-10 logarithm transformation. [b] No adjustment between sDM, nCRDM, sCRDM, SLE, RA, solid cancers, and HC. [c] Adjustment for age between sDM, nCRDM, sCRDM, SLE, RA, solid cancers, and HC. [d] Adjustment for age, disease duration, and immunosuppressive agents using history between sDM, nCRDM, and sCRDM. DM: dermatomyositis; sPD-L1: soluble programmed death ligand 1; sDM: DM without malignancies; CRDM: cancer-related DM; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HC: healthy controls; nCRDM: DM with new-onset cancers; sCRDM: DM with stable cancers.
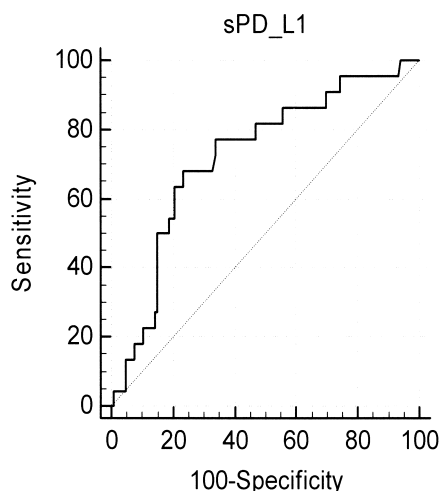
Figure 3. ROC curve analysis for the optimal value of sPD-L1 levels that distinguish patients with nCRDM from sDM patients. ROC: receiver-operating characteristic; sPD-L1: soluble programmed death ligand 1; DM: dermatomyositis; sDM: DM without malignancies; nCRDM: new-onset cancer-related DM.

Table 3. Comparison of 3 ways in diagnosing malignancy. All data are percentages.

	Sensitivity	Specificity	PPV	NPV
sPD-L1[a]	68	76	38	92
anti-TIF1-γ[b]	72	77	40	93
sPD-L1 and anti-TIF1-γ[c]	63	95	70	92

[a] Patients with sPD-L1 concentrations > 16.1 ng/ml alone. [b] Patients who are positive for anti-TIF1-γ antibodies alone. [c] Patients with both sPD-L1 (at a concentration > 16.1 ng/ml) and who are positive for anti-TIF1-γ antibodies. PPV: positive predictive value; NPV: negative predictive value; sPD-L1: soluble programmed death ligand 1; anti-TIF1-γ: antitranscriptional intermediary factor 1-γ.

results are presented in Table 3. The combination of sPD-L1 and anti-TIF1-γ yielded no obvious differences in sensitivity and NPV, but the specificity and PPV rose dramatically, reaching to values of 95% and 70%, respectively.

DISCUSSION

In our present study, we demonstrated that the levels of sPD-L1 increased significantly and extremely high levels of sPD-L1 could be a novel serological marker of malignancy in patients with DM. Measurement of sPD-L1 concentrations could be included in routine clinical practice to evaluate the occurrence of malignancy after a new admission of a patient with DM. Dynamic changes in sPD-L1 levels between active cancers and cancers in remission, as well as cancers before and after treatment, suggested that monitoring sPD-L1 concentrations could be a useful tool for assessing treatment responses in patients with CRDM. Further, specificity and PPV rose dramatically after the union of sPD-L1 and anti-TIF1-γ. Our findings suggested that physicians could consider monitoring those DM patients with both markedly high sPD-L1 levels and anti-TIF1-γ Abs more carefully. Detection of anti-TIF1-γ Ab and sPD-L1 concentrations can single out patients at greater risk of cancer and help them benefit from more extensive malignancy screenings.

For patients with DM, persistent activation of self-reactive immune cells and continuous exposure of type I interferon may be the mechanisms accounting for this significantly increased expression of sPD-L1[25,26,27]. Little is known about the role of PD-L1 in idiopathic inflammatory myopathies. First, Wiendl, *et al* found that PD-L1 was generally expressed on muscle tissues and peripheral blood mononuclear cells in patients with polymyositis (PM), inclusion body myositis, and DM[28]. Later, Xiaoyu, *et al* indicated that PM muscle cells expressed PD-L1 and the expression of PD-L1 correlated with the degrees of muscular necrosis and muscular strength[29]. Wiendl and colleagues hypothesized that human muscle cells could counterbalance the local immune attack and protect muscle fibers from further injury by expressing PD-L1[28]. Further, accumulating data have demonstrated that disruption of the PD-1/PD-L1 pathway accelerates autoimmune disease. PD-1–deficient mice developed SLE-like proliferative arthritis and glomerulonephritis, and dilated cardiomyopathy as well[30,31]. PD-L1^{-/-};MRL-Fas[lpr] mice spontaneously developed autoimmune myocarditis and pneumonitis, indicating that PD-L1 is a critical checkpoint that protects the heart and lung in the autoimmune MRL mouse strains[32]. Also, Wan, *et al* reported that sPD-1 and sPD-L1 occurred at high concentrations in sera and synovial fluid and positively correlated with titers of rheumatoid factor in patients with RA, indicating that the restriction on synovial inflammation in RA was overruled by the excessive production of soluble co-stimulatory molecules[33]. Therefore, it could be speculated that the elevated expression of sPD-L1 may also play a similar immunoregulatory role in DM.

Although the PD-1/PD-L1 pathway can be a negative regulator in the pathogenesis of DM, this pathway can also exert important inhibitory signals that result in ineffective antitumor immunity[10]. There is still little known about the pathogenesis of CRDM development. A few studies suggested that mutation, overexpression, and/or modification of auto antigens on tumor cells may break the immune tolerance and trigger antitumor immune response. Because of cross-reactivity, the antitumor immune responses redirect to normal tissues and organs inappropriately, thereby initiating autoimmunity[34,35]. In our study, markedly higher levels of sPD-L1 were observed in patients with nCRDM than in sDM patients. Our findings raise the possibility that during the DM disease progression, the sPD-L1 levels in some patients may increase beyond a certain threshold, and the excessive immune suppression mediated by the PD-1/PD-L1 pathway may in turn provide assistance in tumor escape and evasion. In addition, we observed that sPD-L1 levels in

patients with nCRDM were much higher than those in patients with sCRDM. The 4 patients who received followup showed a decrease in sPD-L1 levels after curative treatment for cancer, which indicated that sPD-L1 concentrations could differentiate between statuses of malignancy and respond to treatment to some extent.

There are still many problems remaining to be addressed. Some researchers revealed that high levels of sPD-L1 predicted poor outcome in several cancers[17,18,19], but the prognosis has not been established for patients with CRDM who have high sPD-L1 levels. A significant confounding factor in our study is that the types of malignancies among the CRDM cohort vary greatly. It is hard to enroll a sufficient number of patients who share the same type of malignancy. Moreover, the exact association between sPD-L1 and CRDM needs more validation in multicenter studies prior to clinical use.

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