Strong correlation between cancer progression and anti-transcription intermediary factor 1γ antibodies in dermatomyositis patients

M. Ogawa-Momohara[1], Y. Muro[1], T. Mitsuma[2], M. Katayama[3], K. Yanaba[4], M. Nara[5], M. Kakeda[6], M. Kono[1], M. Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Department of Dermatology, Ichinomiya Municipal Hospital, Ichinomiya, Japan; [3]Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan; [4]Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan; [5]Department of Haematology, Nephrology and Rheumatology, Akita University Hospital, Akita, Japan; [6]Department of Dermatology, Mie University, Graduate School of Medicine, Tsu, Japan.

Abstract

Objective

Transcription intermediary factor 1γ (TIF1γ) protein is known as a tumour suppressor that promotes cellular differentiation. Autoantibodies to TIF1γ have a strong clinical association with cancers associated with dermatomyositis (DM). This study aims to identify the clinical characteristics of cancers in anti-TIF1γ antibody-positive adult patients with DM.

Methods

This retrospective analysis covered 160 adult DM patients who visited Nagoya University Hospital or collaborating medical centres between 2003 and 2016. Anti-TIF1γ antibody and other myositis-specific autoantibodies were detected by ELISA. Based on a review of medical charts, the cancers were staged according to the TNM Classification of Malignant Tumours of the Union for International Cancer Control and were divided into the two groups of "advanced" or "non-advanced" according to the stage classification.

Results

Forty-one of the 160 (26%) patients had cancer. The incidence was significantly higher in the anti-TIF1γ-positive patients than in the anti-TIF1γ-negative patients (23/34=68% vs. 18/126=14%, $p<1x10^{-6}$). Anti-TIF1γ-positive patients with cancer were found more frequently in the "advanced" group than in the "non-advanced" group (21/23=91% vs. 9/18=50%, $p<0.0046$). The intervals between DM diagnosis and cancer diagnosis were significantly shorter in the anti-TIF1γ-positive patients than in the anti-TIF1γ-negative patients ($p=0.047$).

Conclusion

Not only did anti-TIF1γ antibodies correlate strongly with malignancy in DM patients, but cancers were also significantly more advanced in anti-TIF1γ-positive DM patients than in anti-TIF1γ-negative patients. Cancers in such cases were very frequently found close to the time of the DM diagnosis.

Key words

advanced cancer, anti-TIF1γ antibody, cancer-associated dermatomyositis, dermatomyositis

Mariko Ogawa-Momohara, MD
Yoshinao Muro, MD, PhD
Teruyuki Mitsuma, MD, PhD
Masao Katayama, MD, PhD
Koichi Yanaba, MD, PhD
Mizuho Nara, MD, PhD
Masato Kakeda, MD, PhD
Michihiro Kono, MD, PhD
Masashi Akiyama, MD, PhD

Please address correspondence to:
Dr Yoshinao Muro,
Division of Connective Tissue Disease and Autoimmunity,
Department of Dermatology,
Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku,
Nagoya 466-8550, Japan.
E-mail: ymuro@med.nagoya-u.ac.jp

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Introduction

Dermatomyositis (DM) is a systemic disease characterised by chronic inflammation in the skin and muscles. An association between DM and malignancy was first reported by Stertz in 1916 (1) and has been widely discussed ever since. Roughly 10–30% of DM patients have a significant risk of malignancy (2). Yang *et al*. reported that the malignancy risk was the highest around the time of DM diagnosis, especially within the first year after the DM diagnosis (3). The affected organs in cancers associated with DM also have been studied (1-4), and they are wide-ranging. Recently, strong associations have been reported between internal malignancy and some myositis-specific autoantibodies (MSA), such as anti-transcription intermediary factor 1γ (TIF1γ) (5) and anti-nuclear matrix protein (NXP-2)/MJ (6) antibodies.

TIF1γ protein is expressed at various levels in several types of cancers and is thought to be a tumour progression suppressor (7, 8). There is the possibility that overexpressed TIF1γ-antigen in cancer might be exposed to the immune system and lead to the production of the autoantibody. Based on this theory, we hypothesised that the more aberrant expression of the antigens in advanced cancers more often leads to the production of anti-TIF1γ antibodies in patients with cancer-associated DM. In this study, we investigated the cancer stages and the periods between DM and cancer diagnoses in anti-TIF1γ-positive or anti-TIF1γ-negative DM patients.

Materials and methods

Ethics statement

Ethical approval for the study was obtained from the individual institutional review boards (Nagoya University, Ichinomiya Municipal Hospital, National Hospital Organization Nagoya Medical Center, Jikei University School of Medicine, Akita University, Mie University), and all sera were collected after the subjects gave their written informed consent.

Patients

Serum samples were obtained from adult Japanese patients with DM followed at each medical centre from 2003 to 2016. Detailed medical histories of every patient were gathered by unified questionnaire. Of the 160 DM patients, 88 patients fulfilled the "definite to probable" criterion of Bohan and Peter (9), and the remaining 72 patients were diagnosed as clinically amyopathic DM according to the criteria proposed by Sontheimer (10).

Cancer

All of the primary cancers were classified according to the International Classification of Diseases for Oncology (ICD-O-3) as follows: oesophageal (C15), stomach (C16), colon (C18-20), breast (C50), ovarian (C56), prostate (C61), bladder (C67), uterine body (C54), oropharyngeal [C01, (C05.1,2), (C09.0,1,9), (C10.0,2,3)], thyroid (C73) and lung (C34) (11).

Cancer staging

All the cancers were staged by the doctor who performed the surgical operation or who diagnosed the cancer at the time of detection. Bladder, oropharyngeal and thyroid cancers, diagnosed between 2003 and 2009, were staged according to the Union for International Cancer Control (UICC) TNM codes (UICC TNM Classification of Malignant Tumors, 6th Edition) (12). Stomach, lung, breast, ovarian, oropharyngeal, bladder, uterine body, prostate and peritoneal cancers, diagnosed between 2009 and 2016, were staged by the UICC TNM 7th Edition (13). Oesophageal and colon cancers, diagnosed between 2003 and 2016, were staged by Japan-specific classifications (14, 15). Stomach cancers, diagnosed between 2003 and 2009, were staged by Japan-specific classifications that were revised in 2010 and that adopt the TNM Classification of Malignant Tumours of the Union for International Cancer Control (UICC TNM classification), 7th Edition (16, 17).

Evaluation of cancer progression

We divided DM patients with cancer into two groups based on cancer progression. The "advanced" group consisted of cancer patients categorised in the UICC stages, which include cases with lymph node metastasis (LNM).

The "non-advanced" group consisted of cancer patients in the UICC stages without LNM. For example, stomach cancer stage IB as determined by UICC TNM 7th includes T2N0M0 and T1N1M0. A patient with T2N0M0 was included in stage IB and categorised in the "advanced" group in this study, because T2N0M0 and T1N1M0 are classified into the same stage.

ELISA

Autoantibodies against NXP-2/MJ, MDA5, TIF1γ, PM/Scl-75/100, Mi-2, SAE1/2, SRP and HMGCR were tested by antigen-capture ELISA according to our published protocols (17). Anti-EJ, Jo-1, KS, PL-7 and PL-12 antibodies were measured by in-house ELISA when the result from anti-ARS commercial kits (MBL, Nagoya, Japan) was positive. For the anti-TIF1γ-positive sera, anti-TIF1α antibodies were also tested by in-house ELISA.

Statistical analyses

Fisher exact probability tests were used to compare frequencies. The Bonferroni correction was applied for some statistics. Mann-Whitney U-tests were used to compare ages. *P*-values of less than 0.05 were considered significant.

Results

Demographic data

One hundred and sixty patients (110 females, 50 males) diagnosed with DM were studied. The patients' ages were 58.7±14.4 (mean ± standard deviation) years. The ages of females and males were 56.3±14.1 years and 63.8±13.5 years, respectively. Forty-one patients (21 females, 20 males) were found to have cancer. Their ages were 67.7±9.5 years (62.9±7.92 in females and 72.7±8.37 in males). The mean follow-up periods of all DM patients after the DM diagnosis was 36.0±38.3 months (0 to 180 months).

Intervals between DM and cancer diagnoses

In 30 of 41 patients complicated with cancer, the malignancy was found after the diagnosis of DM. In the 11 other patients, malignancy findings proceeded the diagnosis of DM. The average interval from the diagnosis of malignancy to the diagnosis of DM was 31.1±30.0 months, and that from the diagnosis of DM to the diagnosis of malignancy was 9.4±27.1 months.

Table I. Clinical features of cancers found in adult patients with dermatomyositis.

Case	Age	Sex	Int.[1]	MSA[2]	Sites/type of malignancies	Cancer stage[3]	Progression[4]	Follow-up[5]
1	65	F	1	TIF1-γ/α	stomach	IIIA	Advanced	16
2	73	M	1	TIF1-γ/α	stomach	III	Advanced	50
3	81	M	2	TIF1-γ/α	stomach	IB	Advanced	14
4	84	M	0	TIF1-γ/α	stomach	II	Advanced	6
5	63	M	-3	TIF1-γ	stomach	IIIC	Advanced	13
6	73	M	0	TIF1-γ	stomach	IV	Advanced	4
7	58	M	1	TIF1-γ	stomach	IV (D)	Advanced	11
8	69	M	1	TIF1-γ/α	lung	IV	Advanced	2
9	69	M	2	TIF1-γ/α	lung	IIIB	Advanced	22
10	69	M	6	TIF1-γ/α	lung	IIA	Advanced	21
11	69	F	-1	TIF1-γ/α	lung	IV	Advanced	1
12	63	F	1	TIF1-γ	lung	IIIA	Advanced	6
13	65	F	-18	TIF1-γ/α	breast	IA	Non-adv.	41
14	51	F	1	TIF1-γ	breast	I	Non-adv.	60
15	67	F	0	TIF1-γ	breast	III	Advanced	4
16	64	F	-2	TIF1-γ/α	ovary	IV	Advanced	3
17	57	F	1	TIF1-γ/α	ovary	IIIC	Advanced	15
18	60	F	18	TIF1-γ/α	peritoneum	NA	Advanced*	28
19	67	F	0	TIF1-γ	peritoneum	IV	Advanced	20
20	58	M	2	TIF1-γ/α	bladder	IV	Advanced	70
21	70	M	-72	TIF1-γ	oesophagus	III L	Advanced	53
22	77	M	1	TIF1-γ	prostate	IV	Advanced	7
23	80	M	2	TIF1-γ/α	SCC	NA	Advanced	10
24	67	F	3	MJ	stomach	IV (D)	Advanced	10
25	76	F	132	MJ	bladder	0is	Non-adv.	72
26	65	F	0	MJ, SAE	uterine body	IVB	Advanced	1
27	77	M	0	SAE	colon	I	Non-adv.	50
28	65	F	0	SAE	oesophagus	IV (D)	Advanced	6
29	49	F	-16	MDA5	ovary	IA	Non-adv.	33
30	55	F	0	MDA5	ovary	IIIC	Advanced	52
31	79	F	-31	MDA5	oropharynx	IV	Advanced	1
32	67	F	81	MDA5	bladder	0a	Non-adv.	156
33	45	F	0	PM/Scl	breast	IIIB	Advanced	5
34	69	M	8	PM/Scl	oropharynx	IV	Advanced	10
35	67	M	17	PM/Scl	prostate	II	Non-adv.	53
36	62	F	1	PL-7	colon	IIIA (L)	Advanced	70
37	62	F	-60	Mi-2	thyroid	I	Non-adv.	67
38	73	M	-15	Mi-2	colon	0	Non-adv.	89
39	79	M	-90	-	bladder	NA	Non-adv.*	18
40	94	M	-29	-	colon	IIA	Non-adv.	1
41	74	M	0	-	pancreas	NA	Advanced*	10

[1]Months between DM diagnosis and malignancy. [2]MSA: myositis-specific autoantibodies. [3]Cancer stage: cancer stage judged according to the UICC 6th and 7th edition, except for cases 7, 21, 24, 28 and 36, which were staged by Japanese criteria. [4]CP: Cancer progression judged by stage, which includes lymph node metastasis (advanced) or not (non-advanced). [5]Months of follow-up after DM diagnosis. *The clinical details are given in the text.
SAE: small ubiquitin-like modifier activating enzyme; MDA5: melanoma differentiation-associated gene 5; ARS: aminoacyl tRNA synthetase; SCC: squamous cell carcinoma; (D): distant metastasis; (L): lymph metastasis; P: positive; N: negative; NA: not available; -: unidentified.

Organs affected by cancer

Of the 41 cancer patients, those with stomach cancer numbered 8, lung cancer 5 (4 small-cell, 1 unknown), colon cancer 4, breast cancer 4, ovarian cancer 4, bladder cancer 4, oropharyngeal cancer 2, prostate cancer 2, oesophageal cancer 2, peritoneal cancer 2, uterine body cancer 1, thyroid cancer 1, pancreatic cancer 1 and unknown primary metastatic squamous cell carcinoma 1. The clinical details of each case are listed in Table I.

Cancer stages and progression

Since Cases 7, 21, 24, 28 and 36 were staged according to Japan-specific classifications, the cancer metastasis status is also listed briefly in Table I. Among the patients with colon cancer, Cases 38 and 40 were not assessed by the Japa-

nese classifications but by the UICC TNM classification according to the surgeons who operated on them. Although the cancer stages of Cases 18, 23, 39 and 41 were uncertain, we divided them into the two groups of "advanced" or "non-advanced according to the clinical data described below. Case 18 had peritoneal cancer with severe abdominal dropsy and received adjuvant chemotherapy, which made cancer staging impossible. Since her cancer extended beyond the pelvic organs after chemotherapy, the cancer had reached at least stage III in the UICC staging, so we included this case in the "advanced" group. Case 23 had squamous cell carcinoma of unknown origin found in mediastinal LNM, which led us to include this case in the "advanced" group. Case 39 was a bladder cancer patient who had been treated with transurethral resection of the bladder tumour (TURBT) without recurrence for 6 years. The stages of bladder cancers for which TURBT is recommended are stages 0 and I (18). Therefore, we included him in the "non-advanced" group. Case 41 received only palliative medication for advanced pancreatic cancer and no investigation to determine the cancer stage. We recognised him as being in an "advanced" stage beyond LNM. In total, 30 of the 41 cases (73.1%) were included in the "advanced" group and the remaining 11 of the 41 cases (26.8%) were included in the "non-advanced" group.

Myositis-specific autoantibodies and cancer incidence

The prevalence of malignancy in groups categorised according to MSA is summarised in Figure 1. The most common MSA in our study was the anti-MDA5 antibody, which was found in 38 patients (24%). Anti-TIF1γ was positive in 34 patients (21%), and the others were as follows: 19 (12%) anti-ARS (6 Jo-1, 5 EJ, 3 PL-7, 3 KS, 2 PL-12), 12 (7.5%) anti-Mi-2, 9 (5.6%) anti-NXP-2/MJ, 7 (4.4%) anti-SAE, 6 (3.8%) anti-PM/Scl, 1 (0.6%) anti-SRP. Only Case 26 in Table I was positive for both anti-NXP-2/MJ and anti-SAE antibodies, and that case is excluded from Figure 1. The incidence of malignancy was significantly higher in the anti-TIF1γ-positive DM patients than in the anti-TIF1γ-negative patients (23/34=68% *vs*. 18/126=14%, $p<1 \times 10^{-6}$) (Fig. 1). We also examined frequencies of cancers in patients with each MSA. Anti-MDA5-positive patients (4/38=11%, $p<0.0001$), anti-ARS-positive patients (1/19=5%, $p<0.0001$) and anti-Mi-2-positive patients (1/12=17%, $p=0.049$) showed statistically significantly lower cancer incidence than anti-TIF1γ-positive patients, even with the Bonferroni correction.

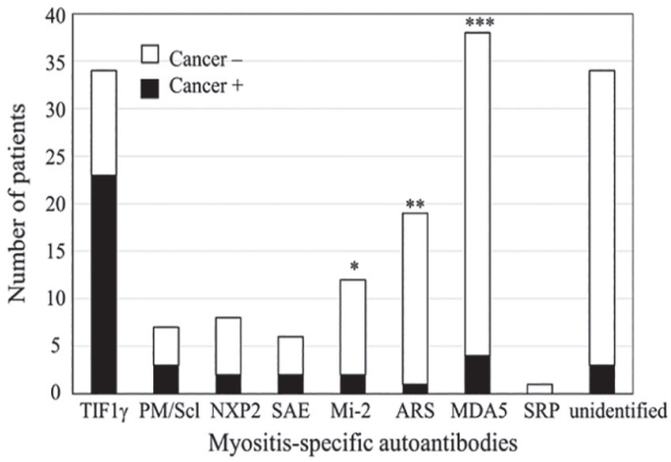

Fig. 1. Cancer complications and myositis-specific autoantibodies in 159 dermatomyositis patients.
*The statistical difference for incidence of malignancy between anti-TIF1γ-positive and anti-Mi-2-positive patients, $p=0.049$ with the Bonferroni correction. **The statistical difference for incidence of malignancy between anti-TIF1γ-positive and anti-ARS-positive patients, $p<0.0001$ with the Bonferroni correction. ***The statistical difference for incidence of malignancy between anti-TIF1γ-positive and anti-MDA5-positive patients, $p<0.0001$ with the Bonferroni correction.
ARS: aminoacyl tRNA synthetase; MDA5: melanoma differentiation-associated gene; MSA: myositis-specific autoantibodies; SAE: small ubiquitin-like modifier activating enzyme; SRP: signal recognition particle.

For the 34 anti-TIF1γ-positive sera, we investigated the simultaneous presence of anti-TIF1α antibody by ELISA. Twenty of the 34 sera (59%) were anti-TIF1α/γ positive. For the 20 anti-TIF1α/γ-positive patients and the 14 anti-TIF1γ positive patients, the cancer incidences were 14 (70%) and 9 (64%) ($p=0.83$), respectively. Patients with "advanced" cancer accounted for 13 of the 14 (92%) anti-TIF1α/γ-positive cancer patients and 8 of the 9 (89%) anti-TIF1γ positive cancer patients ($p=1.00$). The anti-TIF1γ ELISA titres did not statistically differ between the anti-TIF1γ-positive DM patients with *versus* without cancer (106.6±28.8 *vs*. 87.4±48.3, respectively) ($p=0.267$). Although the mean of anti-TIF1γ ELISA titres in the "advanced" cancer group was higher (109.0±30.0, n=21) than in the "non-advanced" cancer group (81.4±8.8, n=2), statistical analysis could not be performed due to the insufficient number of cases.

Cancer progression and other clinical features in the anti-TIF1γ-positive and the anti-TIF1γ-negative groups

We examined the difference in cancer progression, demographic and clinical features between the anti-TIF1γ-positive and the anti-TIF1γ-negative groups. The frequency of "advanced" cancers was significantly higher in the anti-TIF1γ-positive group with cancer than in the anti-TIF1γ-negative group with cancer (21/23=91% *vs*. 9/18=50%, $p<0.0046$) (Table II). No other statistical differences in other clinical features were found between the anti-TIF1γ-positive and anti-TIF1γ-negative groups in Table II.

To identify independently associated factors for the advanced cancer in DM patients, we selected sex, age, interval between DM and malignancy diagnosis, and existence of anti-TIF1γ antibody, for multivariate logistic regression analysis (Table III). The multivariate analysis revealed only anti-TIF1γ presence to be independently associated with advanced cancer in DM.

Anti-TIF1γ antibody and intervals between the diagnoses of DM and cancer

In 18 of the 23 anti-TIF1γ-positive patients with cancer and in 12 of the

18 anti-TIF1γ-negative patients with cancer, malignancies were found after the DM diagnosis. The mean interval from DM diagnosis to cancer diagnosis was 2.2 months in the anti-TIF1γ-positive patients and 20 months in the anti-TIF1γ-negative patients. In the remaining 5 anti-TIF1γ-positive and 6 anti-TIF1γ-negative patients, cancers were found before the DM diagnosis. The mean interval from cancer diagnosis to DM diagnosis was 19.2 months and 40.2 months, respectively.

In light of the closer association of anti-TIF1γ antibodies with cancer occurrence/progression, we next compared the presence of the antibodies with the intervals between DM and cancer diagnoses for 41 DM patients with cancer. A 3-year period of limitation from DM diagnosis is now widely used as the definition of cancer-associated DM (3, 19). However, in our cohorts, most of the anti-TIF1γ-positive cancers with DM were diagnosed within periods much shorter than 3 years (Table IV). Twenty of the 23 (87%) anti-TIF1γ-positive DM patients with cancer were diagnosed within a half-year from DM diagnosis. Anti-TIF1γ-positivity correlated significantly with shorter interval between diagnoses of the two diseases.

Table II. Demographic and clinical features in the adult dermatomyositis patients with cancer in the anti-TIF1γ-positive and the anti-TIF1γ-negative groups.

	anti-TIF1γ-positive n=23	anti-TIF1γ-negative n=18	*p*-value
Male, n (%)	13 (56)	7 (38)	0.64
Age of diagnosis, mean (S.D.), years	67.5 (± 7.9)	68.1 (± 11.2)	0.86
Interval[1] months, median	-0.35	1.5	0.55
Progression[2], n (% of "advanced")	21 (91)	9 (50)	0.0046
Mortality, n (%)	11[+] (52)	6[++] (43)	0.69
Months of follow-up[3], median	20.7	39.1	0.34
Sites/type of malignancies			
stomach	7	1	
lung	5	0	
breast	3	1	
ovary	2	2	
peritoneum	2	0	
bladder	1	3	
oesophagus	1	1	
prostate	1	1	
SCC	1	0	
colon	0	4	
uterine body	0	1	
oropharynx	0	2	
thyroid	0	1	
pancreas	0	1	

[1]Months between DM diagnosis and malignancy. [2]Cancer progression judged by stage, which includes lymph node metastasis (advanced) or not (non-advanced). [3]Months of follow-up after DM diagnosis. [+]Two patients were lost to follow-up. [++]Three patients were lost to follow-up. SCC: squamous cell carcinoma.

Table III. Multivariate analysis assessing the existence of "advanced" cancer.

	Adjusted OR	95 % CI	*p*-value
Sex	0.94	0.13-6.72	0.95
Age	1.02	0.93-1.12	1.02
Interval[1]	1.00	0.98-1.03	1.002
Anti-TIF1γ positive	10.9	1.80-62.11	0.009

[1]Months between DM diagnosis and malignancy. OR: odds ratio, 95% CI: 95% confidence interval.

Table IV. Correlations between anti-TIF1γ antibodies and intervals between cancer and DM diagnoses.

	Interval between cancer and DM diagnosis				
	> ±3yrs	± 2-3yrs	±1-2yrs	±-1yr	± 0-0.5yr
Anti-TIF1γ positive (n)	1	0	2	0	20
Anti-TIF1γ negative (n)	4	2	3	1	8
p-value			0.025		

The *p*-value was calculated by the Fisher exact probability test.

Discussion

We selected methods for comparing cancer progression between anti-TIF1γ-positive and anti-TIF1γ-negative DM patients complicated with cancer. In the UICC TNM system, for consistency, the following categorisations are made, with some exceptions: Stage 0 for carcinoma in situ; Stages I and II for tumours localised to the organ of origin; Stage III for locally extensive tumours, particularly those that have spread to regional lymph nodes; and Stage IV for tumours with distant metastasis (15). The UICC TNM was renewed from the 6th edition to the 7th edition in 2009. Moreover, several cases of cancer were staged by Japanese criteria in our study. In light of this situation, it was difficult to compare cancer progression for all cases only by cancer stage. In this study, we tentatively determined that cancers belonging to stages that include LNM should be categorised as "advanced" cancers. The incidence of "advanced" cancers under our categorisation was significantly higher in anti-TIF1γ-positive DM patients with cancer than in anti-TIF1γ-negative DM patients with cancer. This result suggests that anti-TIF1γ antibodies correlated with cancer progression as well as with cancer incidence. Similar results were reported by Hida *et al*. (20) that, in 36 malignancies complicated with anti-TIF1γ-positive DM, 29 (85%) were at advanced stages (III or IV). However, methods of cancer staging were not described in their study.

We also compared the duration from DM diagnosis to cancer diagnosis between two groups: anti-TIF1γ-positive DM complicated with cancer and anti-TIF1γ-negative DM complicated with cancer. We found negative correlations between the intervals between the diagnoses of the two diseases and anti-TIF1γ antibody positivity. This may

have resulted from the advanced stages of the cancers in the anti-TIF1γ-positive group, as the more advanced cancers would be more easily found. Moreover, in our retrospective study, 76 patients were followed for less than 3 years; thus, it is possible that we might have missed a certain population of cancers that appeared after the 3-year cancer follow-up. However, 10 of the 12 (83%) cancers in anti-TIF1γ-positive patients who received follow-up of more than 3 years were found within a half-year from the DM diagnosis in our cohort. In the previous report (20), anti-TIF1γ-positive cancers, found after the DM onset, were discovered within a year after the DM diagnosis. Thus, we think it is unlikely that we missed a significant number of patients due to insufficient duration of follow-up.

Very recent study has shown that the anti-TIF1γ antibody is not a marker for solid cancers nor for paraneoplastic rheumatic syndrome except in patients with DM (21). Anti-TIF1γ antibodies are also major autoantibodies in patients with juvenile DM who are rarely complicated with malignancies (22). The present study found no significant difference in titres of anti-TIF1γ between the group of DM alone and the group of DM associated with malignancies. According to these findings, anti-TIF1γ antibodies may not be simply induced by the aberrant expression of TIF1γ in cancer. However, the higher anti-TIF1γ titres in the group with advanced cancer than in the group with non-advanced cancer should be investigated further, since anti-TIF1γ antibodies could play a role in the immune pathogenesis of DM associated with cancer.

We also examined cancer incidence in patients with various MSAs. The cancer incidence was the highest in the anti-TIF1γ-positive group (23/35=66%), which is consistent with the results of previous studies (3, 23, 24). Although anti-NXP-2/MJ-positive patients infrequently (2/8=25%) had cancer, a result that was unexpected, anti-SAE and anti-PM/Scl-positive patients showed relatively high cancer incidences (3/7=43% and 2/6=33%, respectively). The further verification of these antibodies as cancer-associated MSA is expected.

There are several other limitations to this study. Some referral bias exists, because some patients were not consecutively seen and were selected only from our country. The results could reflect genetic and geographical factors (4). Uniform methods for cancer screening were not determined in this cohort. For example, clinicians may favor frequent or intensive cancer screening considering MSA results, such as anti-TIF1γ-positivity. To confirm our observations, we need to plan international multicentre prospective studies in the future.

The definition of "advanced" cancers is unique in this study. However, this is the first study that attempts to correlate cancer progression with anti-TIF1γ-antibody status in addition to correlating intervals between diagnoses of DM and cancer. We should clarify whether advanced cancer produces anti-TIF1γ antibodies and induces DM as well. Future prospective investigations with molecular analysis in DM-associated cancer would clarify the aetiology of anti-TIF1γ antibodies in such diseases.

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