Anti-transcriptional intermediary factor 1 gamma antibodies in cancer-associated myositis: a longitudinal study

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Abstract

Objective

To investigate anti-TIF1-γ antibodies in longitudinally followed patients with myositis and cancer.

Methods

Serum levels of anti-TIF1-γ antibodies at different time-points in relation to myositis and cancer diagnosis were analysed by ELISA in 79 patients from a Swedish cohort with polymyositis (PM) and dermatomyositis (DM) and a Spanish cohort restricted to DM patients. Anti-TIF1-γ positive and negative patients were compared with Fisher's exact test, student t-tests and Wilcoxon test.

Results

Thirty-six patients (17 from cohort 1 and 19 from cohort 2) with myositis and cancer were anti-TIF1-γ antibody positive; all had DM. In 88% of anti-TIF1-γ positive patients, cancer was diagnosed within 3 years from DM diagnosis compared to 63% in anti-TIF1-γ negative. Four DM patients, anti-TIF1-γ positive at cancer diagnosis had positive serum samples even antedating cancer diagnosis up to five years. In cohort 1 the median (interquartile range) antibody level was higher, 2.13 au (1.82–2.15), in the seven patients who died <1 year after cancer diagnosis, compared to the seven that died >1 year after cancer diagnosis, 1.34 au (0.92–1.59), (p=0.004). Three patients were still alive and in remission from cancer and DM 14–16 years after cancer treatment of whom two became negative for anti-TIF1-γ antibodies. In the second cohort remission of cancer coincided with remission of DM and low or negative serum levels of autoantibodies.

Conclusion

Anti-TIF1-γ antibodies may be detected before clinical symptoms of cancer and may disappear after successful treatment of cancer with remission of DM supporting DM being a paramalignant phenomenon.

Key words

myositis, dermatomyositis, anti-TIF1-γ antibodies, cancer

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Introduction

Polymyositis (PM) and dermatomyositis (DM), collectively called idiopathic inflammatory myopathies (IIM), are characterised by inflammation of skeletal muscle and clinically by muscle weakness and muscle fatigue. Little is known about causative factors leading to PM or DM but a striking observation first reported in 1916 is the association between malignancies and DM (1, 2). This association was confirmed in large epidemiological studies (3-8) where up to 30% of patients with DM may have cancer. For PM, the association with cancer is weaker (5).

Cancer may precede DM/PM, it may be detected simultaneously, or it may be detected up to 10 years after DM/PM diagnosis (9). It is not clear if cancer leads to myositis or if myositis leads to cancer or if both associations are true or if there are other underlying factors leading to both events. Likewise the pathogenic mechanisms that could explain the association between cancer and myositis are still unclear and different mechanisms may be involved in malignancies that are detected close to myositis diagnosis compared to those that occur more than 10 years after diagnosis of myositis (10).

Until recently, no biomarkers indicating a cancer-associated myositis (CAM) were available. However, recently, two myositis-specific autoantibodies, anti-TIF1-γ, initially reported as anti-p140/155-kDa antibody, and anti-nuclear matrix protein (NXP)2 have been detected in patients with adult DM associated to malignancies (11-17). Thus these myositis-specific autoantibodies (MSAs) could serve as biomarkers for CAM, but the temporal relationship between these antibodies and diagnosis of cancer and myositis is unknown. Moreover, it is not known if the antibodies disappear after successful treatment of a malignancy or if they have a prognostic value for survival after cancer diagnosis. The TIF1 family proteins belong to the TRIM family which are proteins involved in carcinogenesis with positive and/or negative effects. For example, TIF1-α ubiquitinates the tumour suppressor gene p53 and overexpression of this gene in breast cancer is associated with poor prognosis (18). Whether the TIF1 proteins or the anti-TIF1 autoantibodies have a role in the pathogenesis of myositis or cancer-associated myositis is not known but information of anti-TIF1 gamma antibodies levels in relation to cancer diagnosis and prognosis in patients with myositis may shed some light on a possible relationship.

A major aim of our study was to investigate when anti-TIF1-γ antibodies are present in relation to cancer diagnosis and more precisely if (a) anti-TIF1-γ antibodies may precede the diagnosis of cancer (b) whether the antibodies persist or disappear after treatment of the malignancy in patients with CAM and (c) if the antibody levels may predict outcome of malignancy.

Methods

We investigated two patient cohorts, one from Sweden (cohort 1) and one from Spain (cohort 2), with diagnosis of IIM based on Bohan and Peter criteria (19).

Patients included in the Swedish cohort had myositis and cancer at some time point during follow-up. Since one of our objectives was to investigate whether anti-TIF1-γ could be detected in sera taken before or after cancer diagnosis we did not restrict our study population to those diagnosed with cancer within a specific time frame from myositis diagnosis in the Swedish cohort. The Spanish cohort was included to confirm the results from the first cohort and was restricted to patients with DM and cancer diagnosis within five years. Because of different selection criterias, we analysed the longitudinal data from the two cohorts separately.

Cohort 1

Between 1996 and 2012, 170 patients with definite or probable PM or DM (19) visited the rheumatology clinic and were included in the myositis registry at Karolinska University Hospital, Stockholm, Sweden. To identify patients with PM/DM ever having a cancer, the medical records were reviewed at the end of follow-up (January 31 2013) for all patients. Fifty-three (31%) of all patients had ever had a cancer diagnosis. Serum samples and complete clinical data were available from 47 patients that were included in our study.

Table I. Characteristics of patients with myositis and cancer and at least one measurement of anti-TIF1-γ antibody.

	Cohort 1			Cohort 2		
	All n=47	Anti-TIF1-γ pos n=17 (36%)	Anti-TIF1-γ neg n=30 (64%)	All, n=32	Anti-TIF1-γ pos n=19 (59%)	Anti-TIF1-γ neg, n=13 (41%)
Dermatomyositis, n (%)	35 (75)	17 (100)◊	18 (60)	32 (100)*	19 (100)	13 (100)*
Mean (SD) age at myositis in years	58 (14)	64 (14)◊	55 (13)	58 (14)	56 (15)	59 (16)
Mean (SD) age at cancer in years	61 (13)	65 (12)	59 (13)	58 (14)	56 (15)	61 (12)
Women, n (%)	33 (70)	13 (76)	20 (67)	24 (75)	15 (79)	9 (69)
Men, n (%)	14 (30)	4 (24)	10 (33)	8 (25)	4 (21)	4 (31)

*Two patients had amyopathic DM. ◊$p<0.005$ comparing anti-TIF1-γ positive and negative. All other differences did not reach statistical significance.

Twenty-seven of 47 patients had more than one serum sample available for testing; seven patients had two longitudinal samples, 12 patients had three samples, seven had four samples and one patient had five. In 20 patients we were able to identify one or more samples taken from a time point preceding the cancer diagnosis with at least one year. In 25 patients we were able to identify one or more samples taken at least one year after cancer diagnosis.

Cohort 2

As a replication cohort we investigated a Spanish cohort of patients with DM (19) and cancer. Between 1992 and 2016, 199 patients with myositis were identified at the Barcelona Vall d'Hebron Hospital, Spain. Their medical records were reviewed at the end of follow-up (June 30 2016). 139 of them had DM and 34 (17%) had a cancer diagnosis between five years before or after myositis diagnosis. Serum samples were available from 32 of the 34 patients with DM and cancer.

Twenty-four (75%) patients had one serum sample available for testing. Eight of 32 patients had more than one longitudinal samples taken between 1 month and 6 years after cancer diagnosis; two patients had two samples, one had three samples, two had four samples, two had five samples and one patient had seven samples. In one of the patients, the sample preceded cancer with one year.

Clinical data

The following data were retrieved from medical records: sex, age at myositis diagnosis, myositis subdiagnosis, type of cancer, time between myositis diagnosis and cancer, treatment of cancer, presence of metastases, survival after cancer diagnosis and outcome of myositis.

Serum analysis for anti-TIF1-γ antibodies

Sera from both cohorts were tested by ELISA for anti-TIF1-γ antibody levels using a commercially available purified protein (OriGene, Rockville, MD) at Hospital de la Santa Creu i Sant Pau Immunology Lab, Universitat Autonoma de Barcelona, in Barcelona, Spain. The ELISA test was previously compared with anti-p155 antibody detection by protein immunoprecipitation assays with radiolabelled HeLa cells showing excellent agreement. The cut-off for positivity on ELISA was established at 0.209 absorbance units (au); two standard deviations above the mean value for controls (20).

Statistical analysis

To compare binary variables, Chi-square and Fisher's exact tests were used as deemed appropriate. To compare continuous variables that were normally distributed, student *t*-tests were used. To compare continuous variables that weren't normally distributed, Wilcoxon tests were used (Wilcoxon signed-rank test for paired data and Wilcoxon rank sum test for unpaired data). Probability (p) values of <0.05 were considered statistically significant.

Results

Cohort 1: Clinical characteristics and anti-TIF1-γ antibody status

The demographic data are presented in Table I.

Seventeen (36%), all DM, of the 47 myositis patients who had ever had a cancer, were positive for anti-TIF1-γ antibodies, in at least one serum sample taken at any time-point during follow-up. Seventeen (49%) of the DM patients with cancer were anti-TIF1-γ positive.

Fourteen (82%) of the 17 anti-TIF1-γ antibody positive DM patients compared to 17 (57%) (14 DM and 3 PM) of the 30 anti-TIF1-γ negative patients developed cancer within 3 years of myositis diagnosis (Table II, Fig. 1). The locations of cancers are presented in Table II.

Sera antedating cancer diagnosis were available from three of the 17 patients who were ever anti-TIF1-γ positive; all were anti-TIF1-γ positive before cancer diagnosis, up to 5 years before cancer diagnosis (Fig. 2 and Suppl. Table SI). Sera antedating cancer diagnosis were available from 17/30 anti-TIF1-γ negative all being negative. Survival data are summarised in Table II.

When comparing TIF1-γ positive with TIF1-γ negative patients, the TIF1-γ positive patients all had DM and were older than TIF1-γ negative patients, otherwise there were no statistical differences regarding measures of disease prognosis, cancer location, presence of metastases or survival time (Table II).

Cohort 1: Anti-TIF1-γ antibody levels in relation to cancer outcome and levels after cancer diagnosis

The anti-TIF1-γ positive patients who died within one year from cancer diagnosis (n=7) had higher anti-TIF1-γ antibody levels, median 2.13 (IQR 1.82–2.15) au at time of cancer diagnosis compared to the seven patients who died after more than one year, median 1.34 (IQR 0.92–1.59) au (p=0.004, Fig. 3). None of the patients that died later than one year after cancer diagnosis became anti-TIF1-γ negative after cancer diagnosis and the last sample was taken

Table II. Cancer-related characteristics of Cohort 1 and 2.

	Cohort 1			Cohort 2		
	All	TIF1-γ pos	TIF1-γ neg	All	TIF1-γ pos	TIF1-γ neg
Cancer within ±3 years, n (%)	31 (66)	14 (82)	17 (57)	27 (84)	18 (95)	9 (69)
Cancer >3 years before myositis diagnosis, n (%), mean time (y)	3 (6) 4.3	0	3 4.3	1 (3) 3.3	0	1 (8), 3.3
Cancer >3 years after myositis diagnosis n (%), mean time (y)	13 (28), 11	3 (18), 10.6	10 (33), 11.2	4 (13), 4.1	1 (5), 4.7	3 (23), 3.5
Death during follow-up, n (%)	31 (66)	14 (82)	17 (57)	17 (53)	11 (58)	6 (46)
Death within a year of cancer diagnosis, n (%)	14 (30)	7 (41)	7 (23)	7 (22)	4 (21)	3 (23)
Mean (SD) time in years from cancer to death	5.6 (5.4)	4.6 (5.5)	6.1 (5.4)	2.3 (3.0)	2.1 (2.2)	2.8 (4.3)
Death within 5 years of cancer diagnosis, n (%)	27 (57)	13 (77)	14 (47)	15 (47)	10 (53)	5 (38)
Cancer remission during follow-up, n (%)	14 (30)	3 (18)	11 (37)	NA	4 (21)	NA
Gastrointestinal cancer	10 (21)	3 (18)	7 (23)	3 (9)	1 (5)	2 (15)
Ovarial cancer	9 (19)	5 (29)	4 (13)	5 (16)	4 (21)	1 (8)
Other gynae cancer	2 (4)	1 (6)	1 (3)	3 (9)	3 (16)	0
Haematological cancer	5 (11)	1 (6)	4 (4)	1 (3)	0	1 (8)
Breast cancer	8 (17)	2 (12)	6 (20)	10 (31)	7 (37)	3 (23)
Lung cancer	6 (13)	4 (24)	2 (7)	6 (18)	4 (21)	2 (15)
Urinary tract cancer	3 (6)	0	3 (10)	1 (3)	0	1 (8)
Skin cancer	3 (6)	1 (6)	2 (7)	0	0	0
CNS cancer	1 (2)	0	1 (3)	0	0	0
Cancer metastases	27 (57)	9 (53)	18 (60)	NA	7/11 (64) (8 NA)[#]	NA

[#]Information about metastases was available for 11 out of 19 patients. NA: not available. None of the comparisons reached statistical significance.

Table III. Characteristics of myositis patients who were still alive at end of follow-up.

	Cohort 1			Cohort 2◊					
Patient no	P1	P2	P3	P1	P2	P3	P4	P5	P6
Sex	M	F	F	F	F	F	F	F	F
DM year	1999	2001	1993	2013	2014	2011	2006	2009	2016
Age at DM	48	62	47	35	61	34	70	65	54
Anti-TIF1-γ	2001	2001	1996	2013	2014	2011	2007	2014	2015
Pos	2011	2003	2001	2016			2016	2016	2016
Anti-TIF1-γ		2009	2011			2012			
Neg						2015			
Cancer type	Tonsill	Ovarian	Lung	Breast	Lung	Breast	Breast	Breast	Ovarian
Cancer year	1999	2001	2001	2013	2014	2011	2006	1999 2009	2014
Cancer treatment	S, R	S, C	S	S, C, R	C	S, C, R	S	C	S, C
Cancer outcome*	Rem	Rem	Rem	Rem	Partial rem	Rem	Rem	Still active	Still active
Myositis outcome*	Rem	Rem	Rem	Rem	NA	Rem	Rem	Flare	Flare

◊Unavailable data in 2 patients. *Cancer and myositis outcomes assessed at end of follow-up.
Rem: remission; M: male; F: female; Cancer treatment: S: surgery; R: radiation; C: chemotherapy.

1-2 years before death. None of them went into cancer remission before dying and in all patients death was due to the primary cancer or metastases. Three patients were still alive at the end of follow-up, between 14 and 16 years after fulfilled cancer treatment. They were all in remission from cancer and from DM. None of them continued to be treated with immunosuppressive drugs. Two of these patients became negative for anti-TIF1-γ antibodies (initial levels 1.9 au and 0.4 au) and the third had low anti-TIF1-γ level (0.7 au). The clinical features of these three patients are presented in Table III.

Cohort 2: Clinical characteristics and anti-TIF1-γ antibody status

The demographic data are presented in Table I. Two (6%) of the 32 DM patients had amyopathic DM. Nineteen (59%) of the 32 DM patients with cancer were positive for anti-TIF1-γ antibodies in at least one serum sample.

Eighteen (95%) of 19 anti-TIF1-γ antibody positive patients developed cancer within 3 years of DM diagnosis, compared to nine (69%) of the 13 anti-TIF1-γ negative patients (Fig. 1, Table II).

The locations of cancers are presented in Table II. Sera antedating cancer diagnosis were available from one of the 19 anti-TIF1-γ positive patients. This patient was anti-TIF1-γ positive one year before cancer diagnosis and continued to be positive even one year after cancer diagnosis. The patient had

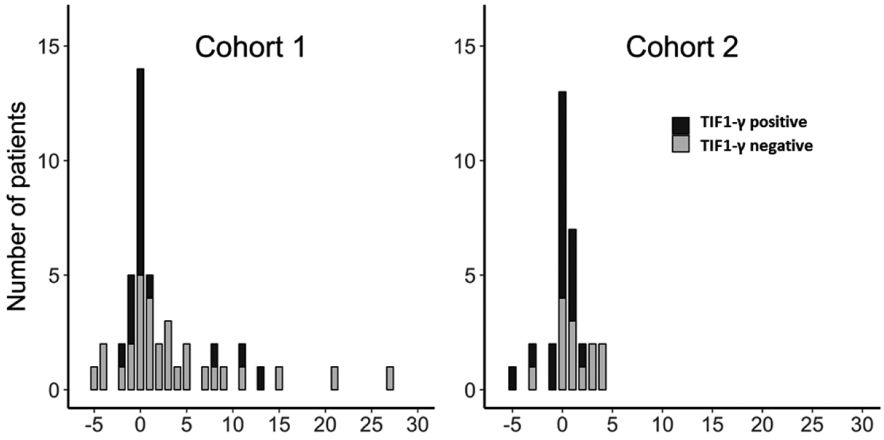

Fig. 1. (original). Time interval in years between myositis diagnosis (Time 0) and cancer diagnoses in patients positive and negative for anti-TIF1-γ antibodies.

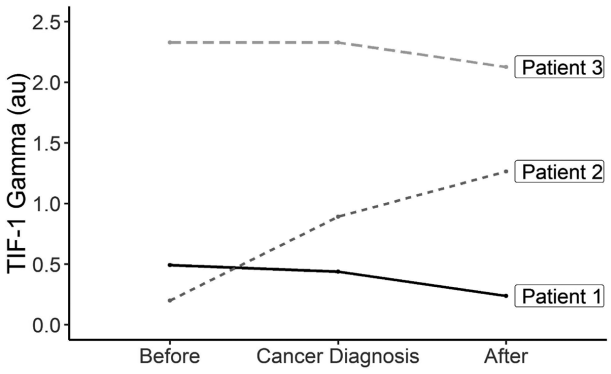

Fig. 2. Levels of anti-TIF1-γ antibodies expressed in absorbance units in three patients from cohort 1 with positive anti-TIF1-γ antibodies and sera available before cancer diagnosis.

an invasive cervical cancer treated with surgery and died two years after cancer diagnosis. Survival data are summarised in Table II. Eleven (58%) of the anti-TIF1-γ antibody positive patients died during follow-up.

When comparing TIF1-γ positive with TIF1-γ negative patients, the TIF1-γ positive patients were slightly older than those negative, but no differences were seen in measures of disease prognosis between the two groups (Table II).

Cohort 2 : anti-TIF1-γ antibody levels in relation to cancer outcome and levels after cancer diagnosis

Eleven (34%) patients, all anti-TIF1-γ positive, had serology data after cancer diagnosis. Four of the 11 anti-TIF1-γ positive patients who died, died within one year from cancer diagnosis. They had a median (IQR) anti-TIF1γ antibody level of 1.31 au (1–1.41) at time of cancer diagnosis. The six patients (one patient had no available data) who died after more than one year had lower antibody levels compared to the four patients who died within one year, with a median (IQR) anti-TIF1-γ antibody level of 0.8 au (0.64–0.89). The difference between the two groups was not statistically significant (p=0.257, Fig. 3). In one patient, the antibody became negative after successful treatment of breast cancer and was still negative after 4 years without cancer or DM relapse. In another patient, the antibody levels followed the clinical course and were lower when the patient had been treated for both cancer and DM and were higher when the patient had a cancer relapse and a flare of DM. In two patients the antibody persisted positive but at lower level even years after cancer treatment and without relapse in cancer or DM (Table III).

Discussion

To our knowledge, this is the first study, including longitudinally collected serum samples over long time intervals, from two independent cohorts of patients with IIM and cancer. We found that anti-TIF1-γ antibodies were associated with DM and cancer diagnosed within three years of DM diagnosis and we discovered that anti-TIF1-γ antibodies can be detected in sera several years before diagnosis of cancer in patients with DM. While previous studies could only discriminate between positive and negative patients, we could follow variation of antibody levels along the years and demonstrate that higher autoantibody titres were associated with higher mortality and that serum levels of antibodies tended to disappear when

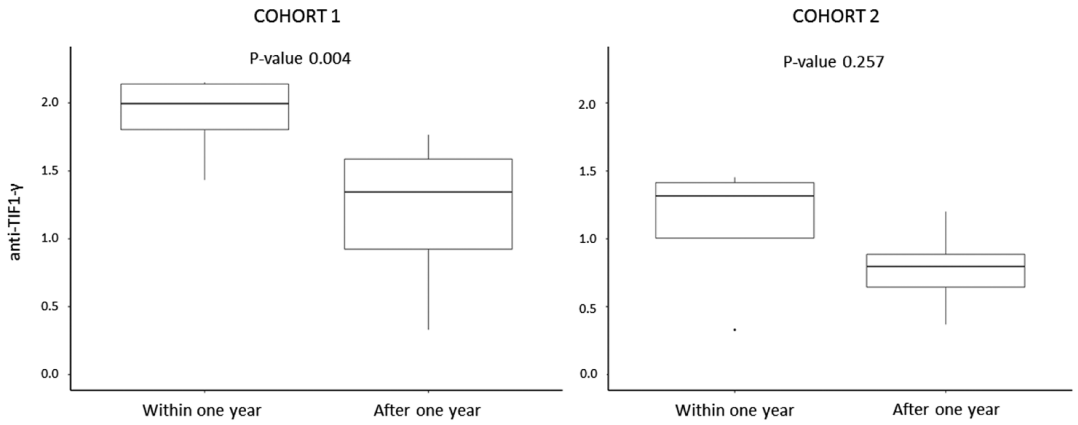

Fig. 3. Serum levels of anti-TIF1-γ antibodies expressed in absorbance units in patients with myositis who died within one year after cancer diagnosis or later in Cohort 1 and Cohort 2.

the malignancy was cured and this coincided with remission of DM.

In our two cohorts of patients with cancer and myositis we found that anti-TIF1-γ antibodies were restricted to adult patients with DM, as has previously been reported (11, 12, 14, 15, 17). In both cohorts, approximately 50% of patients with DM and cancer had anti-TIF1-γ antibodies. Moreover, the cancer associated with anti-TIF1-γ antibodies were in most cases diagnosed within 3 years from DM diagnosis compared to TIF1-γ negative cases where just half of the cancers were diagnosed within 3 years. A close relationship between diagnosis of DM and cancer in TIF1-γ positive was also recently reported (21, 22). The difference between TIF1-γ positive and negative malignancies in relation to onset of DM may suggest that the molecular associations between cancer and TIF1-γ positive DM are different from cancer in TIF1-γ negative DM or PM. In the cases with PM or DM with late onset malignancies both the chronic inflammation and treatment may be involved in the mechanisms that lead to cancer.

In this study, we had a unique possibility to analyse sera in individuals taken before cancer diagnosis. Interestingly, in the 3 individuals with anti-TIF1-γ antibodies where we had sera available before cancer diagnosis these sera were positive for TIF1-γ before cancer diagnosis up to 5 years whereas the patients who were anti- TIF1-γ negative after DM diagnosis were all negative before cancer diagnosis. Despite few cases, our data indicate that anti-TIF1-γ antibodies may be present before clinical symptoms of a malignancy.

In patients where we had samples collected after cancer diagnosis, high anti-TIF1-γ antibody levels seemed to predict a poor survival after cancer diagnosis. On the other hand, in patients who were successfully treated for the cancer, we observed remission of the DM disorder and the anti-TIF1-γ antibody titres became lower or non-detectable. The associations between disease activity of DM and serum levels of anti-TIF1-γ antibody may indicate that these autoantibodies are part of the pathophysiology of cancer-associated DM and that anti-TIF1-γ antibodies represent a molecular link between cancer and the autoimmune disease DM.

The molecular mechanisms between cancer and DM will need further investigations, however. Recently an increased number of genetic modifications, such as mutations and loss of heterozygosity have been demonstrated in TIF1 genes of tumours from patients with anti-TIF1-γ antibody positive myositis and a high expression of TIF1-γ protein was found in tumours, and muscle and skin biopsies of these patients. These observations may suggest that the immune response resulting in anti-TIF1-γ antibodies and DM maybe a physiologic defense against tumours, but this hypothesis will need further investigation (23).

There are limitations in our study, one being some differences between the two cohorts. The Swedish cohort included all patients with PM or DM in whom a cancer had ever been recorded, whereas the Spanish cohort, which was included as a replication cohort, included patients with only DM and cancer within 5 years, and therefore they were analysed separately. However, when we compared the anti-TIF1-γ positive patients between the two cohorts they were remarkably similar. In both cohorts we found that anti-TIF-γ antibodies were mainly present in patients with cancers detected within 3 years of DM diagnosis and that anti-TIF1-γ antibody status may turn negative when the cancer is in remission. However, that high titres conferred worse prognosis could not be confirmed in the second cohort. This could possibly be explained by the overall lower anti-TIF1-γ antibody levels in the second cohort, despite that the serum samples were tested in the same laboratory using the same ELISA test.

From our data we cannot make any recommendations how to follow anti-TIF1-γ positive DM patients without cancer. For this a larger cohort with longitudinal follow-up is needed. In addition, our patients were classified according to the Bohan and Peter criteria as the data were collected before the new EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies were published (24) as these new criteria include variables that we had not retrieved for our cohorts. As we compared patients with DM with or without anti-TIF1-γ antibodies we do not expect that the results would have been much different with the new criteria. Another limitation is that we lacked information about another myositis specific autoantibody known to be associated with DM and cancer, anti-NXP2 antibody, therefore this relationship could not be addressed in our study.

Conclusions

Anti-TIF1-γ antibodies are associated with a diagnosis of cancer within 3 years of DM diagnosis in anti-TIF1-γ antibody positive cases and a positive test for anti-TIF1-γ antibody in adults with DM should alert clinicians to screen carefully for a malignancy. This is supported by the observation of anti-TIF1-γ antibodies were detectable before diagnosis of cancer. However, the risk of an underlying malignancy in anti-TIF1-γ positive patients cannot be answered by our study design. No specific malignancy seems to be associated with anti-TIF1-γ antibodies. Secondly, high levels of anti-TIF1-γ antibodies may be a predictor for poor survival in cancer-associated DM but this needs to be confirmed in a larger cohort. Likewise the clinical relevance of persisting anti-TIF1-γ antibodies after cancer treatment in patients without clinical sings of a persisting malignancy will require investigations in larger cohorts with longer observation time. Thirdly, the temporal relationship between anti-TIF1-γ positive DM and malignancy supports the notion of anti-TIF1-γ positive DM being a paramalignant phenomenon. In contrast anti-TIF1-γ antibody negative cases had a large variation in time frame between diagnosis of cancer and DM or PM which may indicate differences in pathogenic mechanisms in cancer development in anti-TIF1-γ antibody positive and negative cases, which will require further molecular investigations.

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