Association of antinuclear antibody status with clinical features and malignancy risk in adult-onset dermatomyositis

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Background: The clinical significance of antinuclear antibody (ANA) status in adults with dermatomyositis (DM) has yet to be fully defined.

Objective: We compared the incidence of amyopathic disease, risk of malignancy, and clinical findings in ANA^+ and ANA^- patients with adult-onset DM.

Methods: This was a retrospective cohort study of patients with ANA^+ or ANA^- adult-onset DM determined by enzyme-linked immunosorbent assay.

Results: Of 231 patients, 140 (61%) were ANA^+ and 91 (39%) were ANA^-. Compared with the ANA^- patients, the ANA^+ patients had a lower frequency of dysphagia (15% vs 26% [$P = .033$]) and heliotrope rash (38% vs 53% [$P = .026$]). In all, 54 patients (23%) developed malignancy within 3 years of diagnosis of their DM; 11% of the ANA^+ patients developed malignancy versus 43% of the ANA^- patients ($P < .001$). There was a strong association between ANA positivity and lower likelihood of malignancy in multivariable analysis (odds ratio, 0.16; $P < .001$). Conversely, ANA positivity was not associated with amyopathic disease (odds ratio, 0.94; $P = .87$).

Limitations: The retrospective nature of the study was a limitation.

Conclusion: In patients with adult-onset DM, ANA negativity is associated with increased likelihood of development of malignancy within 3 years of diagnosis of their DM. Particularly close follow-up and frequent malignancy screening may be warranted in ANA^- individuals with DM. (J Am Acad Dermatol 2019;80:1364-70.)

Key words: antinuclear antibody; connective tissue disease; dermatomyositis; inflammatory myopathy; malignancy; paraneoplastic.

Dermatomyositis (DM) is a chronic inflammatory disorder with characteristic skin findings and variable degrees of proximal muscle weakness.[1,2] Peak incidence occurs during the fifth decade of life, although individuals of any age may be affected.[3] DM occurs more frequently in

Abbreviations used:

ANA:	antinuclear antibody
DM:	dermatomyositis
ELISA:	enzyme-linked immunosorbent assay
IIF:	indirect immunofluorescence
OR:	odds ratio

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women, with an estimated female-to-male predominance of up to 4:1.[4,5] The disease occurs as a paraneoplastic phenomenon in 13% to 33% of cases.[6-8]

Recent studies have suggested that particular serologic markers, including the myositis-specific antibodies, may help classify patients with DM into more homogenous subgroups that share clinical phenotypes.[8,9] These markers are particularly useful in stratifying patients according to disease prognosis and malignancy risk.[9] Antinuclear antibody (ANA) testing is commonly performed in patients with suspected DM and is positive in 50% to 78% of confirmed cases.[10,11] Unlike the clinical relevance of myositis-specific antibody status, however, the clinical relevance of ANA status in patients with DM has not been well defined. Relevant studies to date are few, have shown conflicting results, and are limited by low statistical power.

CAPSULE SUMMARY

- The result of antinuclear antibody testing is positive in most adults with dermatomyositis.
- There is a strong association between negative antinuclear antibody status and increased risk of underlying malignancy in adults with dermatomyositis. More frequent follow-up and malignancy screening may be warranted in adults with dermatomyositis and a negative antinuclear antibody testing result.

The primary objective of this retrospective review was to determine differences between ANA^+ patients and ANA^- patients with adult-onset DM in terms of incidence of amyopathic disease and malignancy risk within 3 years of diagnosis. As secondary aims, we compared clinical findings between ANA^+ and ANA^- patients and examined the association between amyopathic disease and malignancy within 3 years of diagnosis.

METHODS

After approval by the institutional review board, we conducted a retrospective cohort study of patients in whom DM had been diagnosed at the Mayo Clinic in Jacksonville, Florida, Scottsdale, Arizona, or Rochester, Minnesota, between January 1996 and July 2012. Patients were identified by entering the term *dermatomyositis* into a searchable diagnosis database. Only patients with clinical features and cutaneous histopathology characteristic of DM according to chart review of their dermatology visits were included. Individuals were excluded if they lacked confirmatory skin biopsy data, were less than 18 years of age, or had fewer than 3 years of follow-up. Patients were additionally excluded if they lacked ANA status obtained by enzyme-linked immunosorbent assay (ELISA). ELISA was the preferred method of ANA testing given its automation, standardization, sensitivity comparable to that of classic immunofluorescence-based methods, and continuous numeric reporting scale allowing precise thresholds for determination of ANA status.

After application of the exclusion criteria, the following data were collected from the medical records of 231 patients: age, sex, signs and symptoms of disease, creatine kinase level, aldolase level, presence of interstitial lung disease as determined by pulmonary function testing, and ANA status determined by ELISA at the time of first visit. Signs and symptoms of disease were assumed to be absent if they were not described in the reviewed clinical notes. Patients were considered to have disease-related proximal muscle weakness if it developed at any point within 6 months of their first visit.

Patients were categorized as having amyopathic, hypomyopathic, and myopathic disease. Amyopathic disease was defined as absence of subjective muscle weakness for at least 6 months following diagnosis and a negative or normal result of testing for inflammatory myositis, including measurement of serum creatine kinase and aldolase levels, electromyography, muscle magnetic resonance imaging, or muscle biopsy. Hypomyopathic disease was defined as absence of subjective muscle weakness for 6 months after diagnosis but presence of 1 or more objective markers of inflammatory myositis. Myopathic disease was defined as presence of subjective muscle weakness at any point in the 6 months following diagnosis with 1 or more objective markers of inflammatory myositis. For purposes of determining associations between ANA and amyopathic disease, patients with hypomyopathic and myopathic disease were grouped together.

Data for malignancy occurring within 3 years of diagnosis were recorded. Specifically, we determined the date of malignancy diagnosis, malignancy type, and time from diagnosis of DM to diagnosis of malignancy. Malignancies occurring more than 3 years before or after diagnosis of DM were excluded from analysis.

Statistical analysis

Continuous variables were summarized with the sample median and range, whereas categoric

Table I. Characteristics of all patients and according to ANA status (ANA^+ or ANA^-)

Variable	All patients (N = 231)	ANA^- (n = 91)	ANA^+ (n = 140)	*P* value
Baseline characteristics				
Median age, y (range)	59 (19-89)	59 (24-89)	59 (19-84)	.47
Male sex, n (%)	46 (19.9%)	21 (23.1%)	25 (17.9%)	.33
Interstitial lung disease, n (%)	39 (16.9%)	11 (12.1%)	28 (20.0%)	.12
Signs and symptoms of disease, n (%)				
Proximal muscle weakness	136 (58.9%)	56 (61.5%)	80 (57.1%)	.51
Dysphagia	45 (19.5%)	24 (26.4%)	21 (15.0%)	.033
Arthritis/arthralgia	79 (34.2%)	31 (34.1%)	48 (34.3%)	.97
Pruritus	127 (55.0%)	45 (49.5%)	82 (58.6%)	.17
Scalp involvement	98 (42.4%)	39 (42.9%)	59 (42.1%)	.92
Periungual erythema	97 (42.0%)	36 (39.6%)	61 (43.6%)	.55
Periungual capillary change	102 (44.2%)	37 (40.7%)	65 (46.4%)	.39
Heliotrope rash	101 (43.7%)	48 (52.7%)	53 (37.9%)	.026
Gottron sign	114 (49.4%)	46 (50.5%)	68 (48.6%)	.77
Gottron papules	108 (46.8%)	40 (44.0%)	68 (48.6%)	.49
Holster sign	17 (7.4%)	7 (7.7%)	10 (7.1%)	.88
Shawl sign	51 (22.1%)	26 (28.6%)	25 (17.9%)	.055
Samitz sign	49 (21.2%)	18 (19.8%)	31 (22.1%)	.67
Mechanic's hands	26 (11.3%)	8 (8.8%)	18 (12.9%)	.34
Calcinosis cutis	6 (2.6%)	3 (3.3%)	3 (2.1%)	.59
Cutaneous necrosis	20 (8.7%)	11 (12.1%)	9 (6.4%)	.14
Raynaud disease	30 (13.0%)	10 (11.0%)	20 (14.3%)	.47
Laboratory values, n (%)				
CK level				.089
Elevated	86 (37.2%)	26 (28.6%)	60 (42.9%)	
Normal or low	143 (61.9%)	64 (70.3%)	79 (56.4%)	
Aldolase level				.52
Elevated	95 (41.1%)	36 (39.6%)	59 (42.1%)	
Normal or low	111 (48.1%)	47 (51.6%)	64 (45.7%)	

The sample median (minimum, maximum) is given for continuous variables. *P* values are the result of a chi-square test or a Wilcoxon rank sum test. Information regarding CK level (n = 2) and aldolase level (n = 25) was unavailable.

variables were summarized with number and percentage of patients. Comparisons of baseline characteristics, signs and symptoms of disease, and laboratory values between ANA^- and ANA^+ patients were made by using a Wilcoxon rank sum test for continuous variables and a chi-square test for categoric variables.

To achieve our primary aim, associations of ANA positivity with the separate outcomes of amyopathic disease and malignancy within 3 years of diagnosis were evaluated by using single-variable (ie, unadjusted) and multivariable logistic regression models. In analysis of amyopathic disease, multivariable models were adjusted for all variables that differed between the ANA^+ and ANA^- groups with a *P* value of .05 or lower. For multivariable analysis of malignancy within 3 years of diagnosis, the larger number of patients who experienced this outcome (as opposed to amyopathic disease) allowed for adjustment for all variables that differed between the ANA^+ and ANA^- groups with a *P* value of .05 or lower, as well as by age and sex. Odds ratios (ORs) and 95% confidence intervals were estimated. In a secondary analysis, we examined the association between amyopathic disease and malignancy within 3 years of diagnosis by using a chi-square test. Additionally, the time from diagnosis of DM to malignancy diagnosis was compared according to type of malignancy by using a Kruskal-Wallis rank sum test.

Given that achieving our primary aim entailed performing 2 different tests of association (ie, associations with ANA positivity with both amyopathic disease and malignancy within 3 years of diagnosis), we applied a Bonferroni correction for multiple testing for these primary analyses, after which *P* values of .025 or lower were considered statistically significant. *P* values of .05 or lower were considered significant for all other comparisons that were considered secondary and therefore of a more exploratory nature. All statistical tests were 2 sided. Statistical analyses were performed by using SAS software (version 9.4, SAS Institute, Inc, Cary, NC).

Table II. Summary of primary outcomes in the overall group

Variable	Value (N = 231)
Muscle involvement, n (%)	
Amyopathic	35 (15.2%)
Hypomyopathic	60 (26.0%)
Myopathic	136 (58.9%)
Malignancy diagnosed within 3 y of dermatomyositis diagnosis, n (%)	54 (23.4%)
Median time from dermatomyositis diagnosis to malignancy diagnosis, mo (range)	1.4 (−32.5 to 34.5)
Malignancy type, n (%)	
Gastrointestinal	4 (7.4%)
Breast (females only [n = 41])	11 (26.8%)
Ovarian (females only [n = 41])	12 (29.3%)
Prostate (males only [n = 13])	2 (15.4%)
Thyroid	4 (7.4%)
Lung	6 (11.1%)
Head/neck	1 (1.9%)
Multiple myeloma	2 (3.7%)
Lymphoma	3 (5.6%)
Other	9 (16.7%)

The sample median (minimum, maximum) is given for continuous variables.

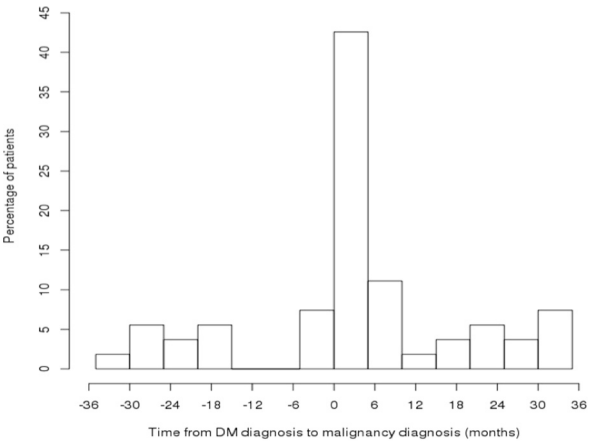

Fig 1. Frequency histogram of time from dermatomyositis (DM) diagnosis to malignancy diagnosis.

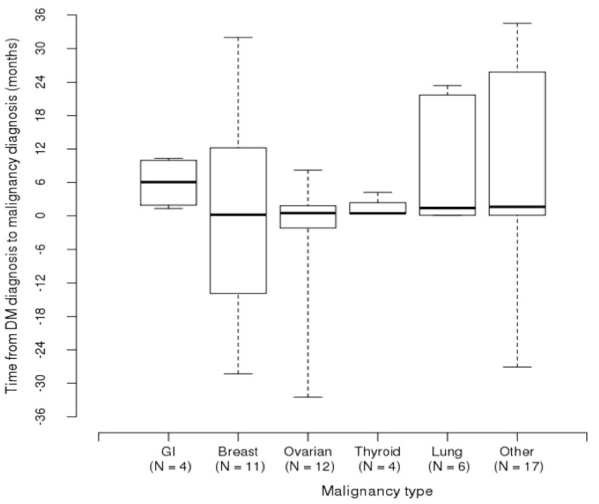

Fig 2. Boxplot of time from dermatomyositis (DM) diagnosis to malignancy diagnosis according to malignancy type. *GI*, Gastrointestinal.

RESULTS

Of the 231 patients, 140 (61%) were ANA$^+$ and 91 (39%) were ANA$^-$. A summary of baseline characteristics, signs and symptoms of disease, and laboratory values is shown in Table I for the overall cohort of 231, as well as separately according to ANA positivity. When compared with the ANA$^-$ patients, the ANA$^+$ patients had lower frequencies of dysphagia (15% vs 26% [P = .03]) and heliotrope rash (38% vs 53% [P = .026]). No other statistically significant differences were observed between the ANA$^-$ and ANA$^+$ groups (all $P \geq .055$ [Table I]).

Outcomes regarding muscle involvement and malignancy are displayed in Table II for the overall group. Amyopathic disease occurred in 35 patients (15%), whereas 60 patients (26%) were hypomyopathic and 136 patients (59%) were myopathic. In all, 54 patients (23%) had malignancy diagnosed within 3 years of diagnosis of their DM. Of these, malignancy was most commonly diagnosed after diagnosis of DM (82%). The median time from diagnosis of DM to diagnosis of malignancy was 1.4 months (range, −32.5 to 34.5 months [Fig 1]), and 54% of all malignancies occurred within 1 year after the diagnosis of DM. The most common malignancy types were ovarian (12 of 41 females [29%]), breast (11 of 41 females [27%]), and lung (6 of 54 patients of either sex [11%]). There was no statistically significant difference in time from diagnosis of DM to diagnosis of malignancy between the different malignancy types (P = .53 [Fig 2]), with only the most frequent malignancy types considered.

An evaluation of the associations of ANA positivity with the 2 separate primary outcomes of amyopathic disease and diagnosis of malignancy within 3 years of diagnosis of DM is shown in Tables III and IV. In single-variable analysis without adjustment, there was no evidence of an association between ANA positivity and amyopathic disease (OR, 1.12; P = .77), and this finding remained consistent in multivariable analysis with adjustment for the potential confounding influences of dysphagia and heliotrope rash (OR, 0.94; P = .87). There was, however, a strong association between ANA positivity and lower likelihood of malignancy within 3 years of diagnosis of DM in both single-variable

Table III. Association of ANA positivity with amyopathic disease

ANA status	Fraction (%) of patients with amyopathic disease	Single-variable analysis		Multivariable analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Negative	13/91 (14.3%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Positive	22/140 (15.7%)	1.12 (0.53- 2.35)	.77	0.94 (0.43-2.03)	.87

ORs, 95% CIs, and *P* values are the result of logistic regression models. For associations between ANA status and amyopathic disease, multivariable models were adjusted for all variables that differed between ANA^- and ANA^+ patients with a *P* value of .05 or lower (dysphagia and heliotrope rash).
ANA, Antinuclear antibody; *CI*, confidence interval; *N/A*, not applicable; *OR*, odds ratio.

Table IV. Association of ANA positivity with diagnosis of malignancy within 3 years of diagnosis of DM

ANA status	Fraction (%) of patients who received a diagnosis of malignancy within 3 y of diagnosis of DM	Single-variable analysis		Multivariable analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Negative	39/91 (42.9%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Positive	15/140 (10.7%)	0.16 (0.08- 0.32)	<.001	0.16 (0.07-0.34)	<.001

ORs, 95% CIs, and *P* values are the result of logistic regression models. For associations between ANA status and diagnosis of malignancy within 3 years of diagnosis of DM, multivariable models were adjusted for all variables that differed between ANA^- and ANA^+ patients with a *P* value of .05 or lower (dysphagia and heliotrope rash), as well as by age and sex.
ANA, Antinuclear antibody; *CI*, confidence interval; *DM*, dermatomyositis; *N/A*, not applicable; *OR*, odds ratio.

analysis (OR, 0.16; $P < .001$) and multivariable analysis (OR, 0.16; $P < .001$); 43% of ANA^- patients developed malignancy within 3 years of diagnosis of DM compared with only 11% of ANA^+ patients. All results remained consistent with adjustment of the multivariable logistic regression models individually for other baseline characteristics, signs and symptoms of disease, and laboratory values to account for any remaining confounding potential of these variables (data not shown).

There was no evidence of an association between amyopathic disease and malignancy within 3 years of diagnosis of DM ($P > .99$). Specifically, 23% of patients with amyopathic disease developed malignancy compared with 24% of patients with hypomyopathic/myopathic disease.

DISCUSSION

ANA testing is a frequently ordered laboratory study in patients with suspected DM, and the result may be positive in more than 50% of confirmed cases.[10,11] However, the clinical significance of ANA status in these patients is unknown. Few reports have rigorously investigated the association of ANA status with features of DM, and those that have done so have produced conflicting results with small sample sizes.[7,12,13] The objectives of our study were to better characterize the differences between ANA^+ and ANA^- patients with adult-onset DM with respect to incidence of amyopathic disease, risk of malignancy within 3 years of diagnosis of their DM, and clinical findings.

DM occurred with a female predominance of 4:1 in this study cohort. The result of ANA testing was positive in 140 patients (61%), which is similar to the 50% to 78% rate of positivity found in prior series.[10,11] Individuals with a positive ANA test result had lower frequencies of dysphagia and heliotrope rash than ANA^- patients did. There were no other significant differences in clinical findings between the ANA^+ and ANA^- groups. Dysphagia has been shown to occur more frequently in the paraneoplastic form of DM, and it is possible that this feature was more strongly associated with negative ANA status in our study because those individuals were also more likely to have an associated malignancy. A recent study of patients with adult-onset DM did not show any significant differences in cutaneous findings based on ANA status, including heliotrope rash.[13]

The association between ANA status and amyopathic disease was also investigated. Overall, 15% of patients were classified as amyopathic. This rate is in agreement with population-based studies suggesting that 5% to 20% of all patients with DM are amyopathic.[4,14] We found no significant difference between incidence of amyopathic disease in the ANA^+ and ANA^- groups. Although the relatively limited number of amyopathic patients in this cohort could limit detection of an association with ANA positivity, this finding is corroborated by another study.[10]

The association between DM and malignancy is well established in the literature, with an estimated 13% to 33% of patients with DM identified as

paraneoplastic.[6-8] Although type of malignancy is variable, ovarian cancer has consistently been shown to be over-represented.[15,16] Our study confirmed these results; a total of 54 patients (23%) developed malignancy within 3 years of diagnosis of their DM, with ovarian malignancy being most common (29% of females). The next most common malignancies were breast (27% of females) and lung (11% of patients of either sex).

Our data show that ANA^- individuals are significantly more likely to have an associated malignancy within 3 years of diagnosis than ANA^+ patients are. Although studies regarding ANA status and malignancy risk in DM are scarce, Nishikai and Sato[12] found similar results in their report of 36 patients with adult-onset DM. In that study, the incidence of malignancy was significantly higher in ANA^- individuals than in ANA^+ patients (53% vs 13% [$P < .001$]). A more recent study showed no association between ANA status and cancer risk, but that report included only 6 patients with malignancy.[7] Importantly, ANA was determined by indirect immunofluorescence (IIF) in these prior studies, and whether their results would have differed had the ANA determinations been made through ELISA is unknown.

Why negative ANA^- status might be associated with the paraneoplastic form of DM is unclear. However, it may suggest that the pathophysiology of DM occurring in the setting of malignancy is distinct from that of the classic idiopathic form, and that a different serologic background is involved. A recent study by Chen et al,[8] for example, showed that levels of soluble programmed death ligand 1 were significantly increased in patients with paraneoplastic DM compared with in controls. The authors proposed that soluble programmed death ligand 1 secreted by tumor tissue played a role in decreasing antitumor immunity in these patients and may have secondarily incited a DM-like eruption through unknown mechanisms. A variety of other tumor-derived biologic mediators, including hormones, peptides, cytokines, and antibodies, have also been implicated in the pathogenesis of paraneoplastic DM.[17]

In our study, 82% of patients with paraneoplastic DM developed their malignancy after the diagnosis of DM, and more than half of the malignancies occurred within the first year of diagnosis. There were no apparent differences in timing of malignancy diagnosis with respect to diagnosis of DM across malignancy types. These findings are in agreement with those of prior series showing that malignancy risk is greatest within the first 1 to 2 years following diagnosis of DM, regardless of malignancy type.[18,19] A recent study additionally showed that 59% of patients with paraneoplastic DM had no symptoms related to their malignancy, and that most were identified through screening computed tomography scans.[18] Taken together, these data illustrate the importance of establishing objective serologic markers that help identify patients at greatest risk of malignancy at the time of diagnosis of DM. The only currently established laboratory indicators of increased malignancy risk in patients with DM are anti—transcription intermediary factor 1 gamma, anti—nuclear matrix protein 2, and elevated erythrocyte sedimentation rate.[20] Our results suggest that negative ANA status may serve as an additional marker of increased cancer risk.

Recently developed evidence-based malignancy screening guidelines propose that all patients with newly diagnosed DM undergo colonoscopy and low-dose chest computed tomography and that all women with newly diagnosed DM undergo Papanicolaou smear, transvaginal ultrasound, and mammography.[21] Guidelines for subsequent malignancy screening, however, have not been well defined. Some authors have advocated for repeat imaging studies even in the absence of symptoms, with suggested testing intervals varying from every 3 to 12 months over periods of 2 to 5 years.[19,22] Although determination of exact screening frequencies requires consideration for cost among other factors, our study suggests that repeat imaging studies at regular and frequent intervals may be warranted in ANA^- individuals with DM for a period of 2 years, especially in the setting of treatment-resistant or relapsed disease. Although imaging alone is insufficient to detect all types of malignancy that may develop in DM, these tests are effective screening tools for the most commonly diagnosed cancers in the studied cohort (ovarian, breast, and lung).

We also investigated associations between amyopathic disease and malignancy within 3 years of diagnosis of DM. No difference was found in malignancy risk between the amyopathic and myopathic groups, which is consistent with the findings of previous reports.[4,7,14]

A main limitation of our study was its retrospective nature. This may have particularly affected data regarding signs and symptoms of disease present at the initial visit. It is possible that some of these characteristics were inadequately documented, thereby underestimating their true frequencies. Another limitation is that we considered only malignancies developing within 3 years of diagnosis of DM to be paraneoplastic. This time frame was selected because prior reports have

consistently shown that the risk of DM-associated cancers is highest during this window.[16,19,20] Chow et al, for example, showed that malignancy risk is elevated 6-fold and 2-fold within 1 and 2 years of diagnosis of DM, respectively, with no significantly increased risk after 3 years following the diagnosis.[16] Similarly, Chen et al found standardized incidence ratios for comorbid malignancies of 21.3 and 5.1 within 1 and 2 years of diagnosis of DM, respectively, with the risk continuing to decline with subsequent follow-up.[19] Whether our results would differ if malignancies developing more than 3 years before or after diagnosis of DM were considered is unknown.

Another limitation is that we made no adjustment for multiple testing when making comparisons of clinical features between groups owing to the secondary nature of these comparisons. Finally, generalization of our results to patients with ANA determined by IIF may be limited because only patients with ANA testing by ELISA were included. Our results, however, are expected to become generalizable to a larger population over time, as IIF is being increasingly replaced by ELISA and other automated multiplex assays given their objectivity, reproducibility, ease of use, and reduced cost.[23-26]

In conclusion, in patients with adult-onset DM, ANA negativity is strongly associated with the development of malignancy within 3 years of diagnosis. Although malignancy screening is obligatory in all cases of DM, closer follow-up and more frequent laboratory or imaging diagnostics may be warranted in ANA$^-$ patients.

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