HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2017 November ; 69(11): 1771–1776. doi:10.1002/acr.23188.

Dermatomyositis Patients with Anti-Nuclear Matrix Protein-2 Autoantibodies Have More Edema, More Severe Muscle Disease, and Increased Malignancy Risk

Jemima Albayda[*],
Johns Hopkins University School of Medicine, Baltimore, MD

Iago Pinal-Fernandez[*],
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Wilson Huang,
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Cassie Parks,
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Julie Paik,
Johns Hopkins University School of Medicine, Baltimore, MD

Livia Casciola-Rosen,
Johns Hopkins University School of Medicine, Baltimore, MD

Sonye K. Danoff,
Johns Hopkins University School of Medicine, Baltimore, MD

Cheilonda Johnson,
Johns Hopkins University School of Medicine, Baltimore, MD

Lisa Christopher-Stine, and
Johns Hopkins University School of Medicine, Baltimore, MD

Andrew L. Mammen
Johns Hopkins University School of Medicine, Baltimore, MD

National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Abstract

Address correspondence to Andrew L. Mammen, M.D., Ph.D., Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Expression, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, 50 South Drive, Room 1146, Building 50, MSC 8024, Bethesda, MD 20892. andrew.mammen@nih.gov. Phone: 301-402-6956. Fax: 301-594-0305.
[*]These two authors contributed equally to this work.

Objectives—Dermatomyositis (DM) patients typically present with proximal weakness and autoantibodies that are associated with distinct clinical phenotypes. We observed that DM patients with autoantibodies recognizing the nuclear matrix protein NXP-2 often presented with especially severe weakness. The aim of this study was to characterize clinical features associated with anti-NXP-2 autoantibodies.

Methods—235 DM patients underwent testing for anti-NXP-2 autoantibodies. Patient characteristics, including muscle strength, were compared between those with and without these autoantibodies. The number of cancer cases observed in anti-NXP-2-positive subjects was compared with the number expected in the general population.

Results—56 (23.8%) of the DM patients were anti-NXP-2-positive. There was no significant difference in the prevalence of proximal limb weakness in patients with and without anti-NXP-2. In contrast, anti-NXP-2-positive patients had more prevalent weakness in the distal arms (35% vs. 20%, p=0.02), distal legs (25% vs. 8%, p<0.001), and neck (48% vs. 23%, p<0.001). Anti-NXP-2-positive subjects were also more likely to have dysphagia (62% vs. 35%, p<0.001), myalgia (46% vs. 25%, p=0.002), calcinosis (30% vs. 17%, p=0.02) and subcutaneous edema (36% vs. 19%, p=0.01) than anti-NXP-2-negative patients. Five (9%) anti-NXP-2-positive subjects had cancer-associated myositis, representing a 3.68-fold increased risk (95% confidence interval 1.2-8.6) compared to the expected prevalence in the general population.

Conclusions—In DM, anti-NXP-2 autoantibodies are associated with subcutaneous edema, calcinosis, and a severe muscle phenotype characterized by myalgia, proximal and distal weakness, and dysphagia. As anti-NXP-2 positive patients have an increased risk of cancer, we suggest they should undergo comprehensive cancer screening.

Keywords

Dermatomyositis; Myositis; Cancer; Calcinosis; Edema

INTRODUCTION

Dermatomyositis (DM) typically presents with proximal muscle weakness, skin rashes, and autoantibodies. Each DM-associated autoantibody recognizes one of several different proteins including Mi-2, transcription intermediary factor 1γ (TIF-1γ), melanoma differentiation-associated protein 5 (MDA-5), and nuclear matrix protein 2 (NXP-2). Interestingly, each of these autoantibodies is associated with a distinct clinical phenotype.

Anti-NXP-2 autoantibodies were first described in juvenile DM (1) and have subsequently been described in adult DM (2-4). In both juvenile and adult DM, anti-NXP-2 autoantibodies have been associated with calcinosis cutis (5-7). In studies of adult DM patients, it has been suggested that anti-NXP-2 autoantibodies may be associated with malignancy (2, 8). However, in a multivariate analysis, the association between cancer and antibodies to NXP-2 did not reach statistical significance.

We noticed several anti-NXP-2-positive patients who presented with muscle pain, subcutaneous edema, dysphagia, and both proximal and distal muscle weakness. In this

study, we have compared the prevalence of these clinical features – along with other features – in a large number of adult DM patients with and without anti-NXP-2 autoantibodies.

PATIENTS AND METHODS

Study population and anti-NXP-2 testing

Patients evaluated between 2002 and 2015 at the Johns Hopkins Myositis Center were enrolled in a longitudinal study and included in the current study if they met Bohan and Peter's criteria for definite or probable dermatomyositis (9), Sontheimer's criteria for amyopathic dermatomyositis (10), and/or had dermatomyositis by muscle biopsy according to ENMC criteria (11) and subsequently underwent testing for anti-NXP-2. Anti-NXP-2 testing was performed as previously described by immunoprecipitating ^{35}S methionine-labeled NXP-2 protein generated by *in vitro* transcription and translation (8) and/or by immunoprecipitation through the Oklahoma Medical Research Foundation.

Muscle strength at the first clinical visit was prospectively graded in 15 muscle groups using the Medical Research Council (MRC) scale. This scale was transformed to a modified Kendall's 0-10 scale for analysis purposes as previously described (12). Proximal arm muscle groups included the arm abductors, elbow flexors, and elbow extensors. Distal arm muscles tested included the wrist flexors, wrist extensors, finger flexors, and finger extensors. Hip flexors, hip extensors, knee flexors, and knee extensors were tested as proximal leg muscles. Ankle dorsiflexors and plantar flexors were included among the distal leg muscles. Neck flexor and neck extensor strength was also tested.

Other clinical features were obtained by retrospective chart review. Subcutaneous edema was defined as pitting or non-pitting extremity edema accompanying the active phase of the disease. Dysphagia and myalgia were determined by patient report. Interstitial lung disease (ILD) was defined through a multidisciplinary approach suggested by the American Thoracic Society (13). Data for malignancy and calcinosis were obtained up to the last visit. Thigh muscle magnetic resonance imaging (tMRI) and analysis was performed as previously described (14).

Statistical analysis

Dichotomous variables were expressed as percentage and absolute frequency. Continuous features were reported as mean and standard deviation (SD). Creatine kinase (CK) was expressed as median, first, and third quartile for descriptive purposes and transformed through a base-10 logarithm for regression analysis. Univariate and multivariate comparisons between groups were made using logistic regression to compare bivariate variables and linear regression to compare continuous variables. Candidate confounding variables were included in the multivariate analysis if they showed significant differences between groups in the univariate analysis. Given that the duration of the disease could influence variables related with the evolution of disease, the time from the onset of the disease to the first visit at Hopkins was included in the multivariate analysis even if no differences were found regarding this variable in the univariate analysis.

As previously described (Tiniakou E, *Rheumatology*, in press), indirect standardization was used to compare the number of cases of cancer observed in our sample during three years before or after disease onset with the number of cases expected in the general population with the same age and sex distribution using data from the 2008-2012 United States Cancer Statistics registry, available at the Center for Disease Control and Prevention.

All statistical analyses were performed using Stata/MP 14.1. Because this was an exploratory study, a 2-sided p value of 0.05 or less was considered significant, with no correction for multiple comparisons.

RESULTS

Demographic features of study subjects

Of 235 DM patients included, 56 (23.8%) were positive for anti-NXP-2 autoantibodies and 179 (76.2%) were negative. From among the 179 anti-NXP-2 negative patients, 99 (55%) were positive for another myositis autoantibody; 26 (26%) had anti-TIF1γ (26%), 25 (25%) had anti-Mi2, 22 (22%) had anti-Jo1, 13 (13%) had anti-Pm/Scl, 7 (7%) had anti-MDA5, and the remainder had autoantibodies found in less than 5% of the sample. There were no significant differences between the two groups in terms of age at onset of disease, sex, or race (Table 1). Furthermore, there was no significant difference in the time between symptom onset and evaluation of muscle strength when comparing those with and without anti-NXP-2 autoantibodies.

Manifestations of muscle involvement in DM patients with and without anti-NXP-2 autoantibodies

On average, anti-NXP-2 positive subjects had more severe muscle weakness in most muscle groups (see Supplementary Table 1). Although there was a trend for more anti-NXP-2 positive patients to have proximal arm and leg weakness, this did not reach statistical significance (Table 2). In contrast, more anti-NXP-2-positive patients had distal arm weakness (35% vs. 20%, $p=0.02$) and distal leg weakness (25% vs. 8%, $p<0.001$) than those without this autoantibody (see Supplementary Table 2 for the prevalence of weakness by individual muscle group). Compared with anti-NXP-2 patients, no autoantibody group showed increased lower extremity distal weakness. The only autoantibody group with greater prevalence of weakness in the upper distal muscles was anti-Pm/Scl (6 of 8; 46%). Anti-NXP-2-positive patients also had more neck weakness than anti-NXP-2-negative patients (48% vs. 23%, $p<0.001$). Furthermore, the anti-NXP-2-positive subjects were more likely to present with myalgias (46% vs. 25%, $p=0.002$) and develop dysphagia (62% vs. 35%, $p<0.001$; see Table 3). However, the CK levels documented near the time of muscle strength testing were no different between those with and without anti-NXP-2 autoantibodies. Of note, there was no evidence for more diaphragmatic weakness in the anti-NXP-2-positive group; the mean FVC exceeded 85% of predicted in both those with and without this autoantibody (regardless if they presented with ILD or not).

Consistent with our prior study (15) muscle biopsies from both anti-NXP-2-positive and –negative patients had equivalent rates of perifascicular atrophy and perivascular

inflammation (32% vs 49% and 53% vs. 62%; both p>0.05). As previously noted, there was an absence of lymphocytic invasion of muscle fibers (i.e., primary inflammation) in muscle biopsies from the anti-NXP-2-positive patients (0%) compared to the anti-NXP-2-negative group (31%, p=0.005).

We also analyzed tMRI findings and found that the extent of muscle atrophy (percentage of muscles showing atrophy) was increased in anti-NXP2 positive patients compared to those without this antibody (29% vs. 11%, p=0.02). In contrast, there was no significant difference in the extent of muscle edema, fatty replacement of muscle, or fascial edema between these two groups.

Extramuscular manifestations of disease in DM patients with and without anti-NXP-2 autoantibodies

Subcutaneous edema occurred in 36% of patients with anti-NXP2 autoantibodies and in only 19% of anti-NXP-2-negative patients (p <0.01; see Table 3). The prevalence of edema was 17% for anti-TIF1γ, 12% for anti-Mi2, 18% for anti-Jo1, 21% for anti-PM/Scl, and 0% for anti-MDA5. None of these other myositis autoantibodies were associated with an increased prevalence of edema.

Among all DM subjects, 54 out of 235 (23%) presented with subcutaneous edema. Among these, those who presented with edema also had more significant weakness in the neck (8.9 vs. 9.6 strength points, p<0.001), proximal arms (8.4 vs. 9.1, p=0.002), distal arms (9.6 vs. 9.8, p=0.009), proximal legs (9.1 vs. 9.5, p=0.03), and distal legs (9.7 vs. 9.9, p=0.002). Interestingly, patients with edema showed significantly more necrosis (42% vs. 12%, p=0.005) and less primary inflammation on muscle biopsy (5% vs. 30%, p=0.03).

ILD was diagnosed in 7% of anti-NXP-2-positive patients and in 28% of the anti-NXP-2-negative group (p=0.002). The severity of the ILD, as measured by the percent of predicted FVC, was mild in both groups and not significantly different between those with and without anti-NXP-2 autoantibodies (87% vs. 77%, p=0.4). While the ESR was slightly increased in those with anti-NXP-2 autoantibodies (35.2 vs. 23.2 mm/hr, p=0.02), neither those with or without this antibody had markedly elevated inflammatory markers.

Calcinosis was more common in adult patients with anti-NXP-2 autoantibodies (30% vs 17%, p=0.02). Among these patients, there was no association between calcinosis and subcutaneous edema. Anti-NXP-2 positive patients with calcinosis did not have increased weakness compared to those without calcinosis (all p>0.05).

The prevalence of malignancy in DM patients with anti-NXP-2 autoantibodies

There were 5 cases of cancer in the anti-NXP-2-positive patients during the three years before or after the onset of the disease (papillary carcinoma, clear cell renal carcinoma, colon adenocarcinoma, non-small lung carcinoma and Waldenstrom's macroglobulinemia). Compared with the expected number of cancers for patients in the general population of the same age and gender (1.36 cases), patients with anti-NXP2 were found to have a 3.68-fold increased risk of cancer (95%CI 1.2-8.6). There was no difference in the prevalence of

cancer-associated myositis between those with and without anti-NPX2 autoantibodies (9% vs. 8 %, p=0.9) (Table 3).

Excluding anti-Jo1 and Pm/Scl patients from the analyses

Since there remains some debate regarding whether patients with anti-Jo1 and anti-PM-Scl autoantibodies should be included among those with DM, we performed all the statistical analyses found in Tables 1-3 after excluding these patients (data not shown). The results were remarkably similar and our conclusions remained unchanged.

DISCUSSION

In adult DM, the prevalence and clinical associations of anti-NXP-2 autoantibodies have varied considerably between different studies. Using a cohort from the United Kingdom and Prague, only 3% of adult patients with myositis had anti-NXP2 autoantibodies; these were found exclusively in DM patients (3). There was no cancer seen in this group and only one patient had calcinosis. However, there was a high frequency of interstitial lung disease (64%) in this small group of patients. In an Italian cohort, autoantibodies against NXP-2 were the most prevalent myositis-specific antibody (17%) and calcinosis was present in about 30% of patients with this immunospecificity. No interstitial lung disease or malignancy was noted in these patients, who tended to be younger and responsive to treatment. Of note, in a Japanese cohort of 507 myositis patients, only 7 patients with DM (1.6%), and 1 with PM (1.6%) were anti-NXP-2-positive (2). Among these 8 patients, half were noted to have advanced stage malignancy close to the time of diagnosis. This association with malignancy in adult myositis was further supported by a study in the United States showing that majority of cancer-associated myositis was accounted for by patients with antibodies recognizing either NXP-2 or TIF1γ; however, a definite association with anti-NXP-2 autoantibodies alone could not be demonstrated (8).

In the current study, we focused on skeletal muscle involvement in anti-NXP-2-positive patients. These patients had significantly more severe muscle weakness in most muscle groups tested. They were also more likely to have muscle pain and dysphagia, which may reflect more severe muscle disease activity. Although anti-NXP-2-positive and -negative subjects had a similar prevalence of proximal weakness, a higher proportion of autoantibody-positive subjects also had distal weakness. It could be that distal weakness simply reflects greater disease severity in the anti-NXP-2-positive group. However, some patients had severe finger extensor weakness despite relatively better-preserved strength in the elbow flexors and extensors. Similarly, some patients had ankle dorsiflexor weakness exceeding that seen in the knee extensors and flexors. These observations suggest that distal muscles may be more susceptible to damage in anti-NXP-2 positive subjects.

We cannot definitively explain why anti-NXP-2 positive patients are generally weaker than anti-NXP-2 negative patients in the context of similar mean CK levels. However, in the current study we confirmed our prior findings that (a) anti-NXP-2 positive DM patients have perivascular inflammation and perifascicular atrophy which could cause muscle dysfunction without elevating CK levels and (b) unlike anti-NXP-2 negative patients, anti-NXP-2 positive patients have no lymphocyte invasion of muscle fibers which would be expected to

disrupt the myofiber membrane and result in increased serum CK levels. Furthermore, in the current study, we found that tMRIs showed increased muscle atrophy in anti-NXP-2 positive patients compared to anti-NXP-2 negative patients. Of note, muscle atrophy may cause weakness without increasing CK levels. Taken together with the muscle biopsy features, these radiographic findings suggest that the mechanisms of muscle damage causing muscle weakness may be different in anti-NXP-2 patients compared to other DM patients. We hypothesize that these mechanisms may result in greater weakness even in the context of equivalent CK levels.

Subcutaneous edema is not a well-characterized feature of patients with DM. Indeed, a literature review yielded just 26 cases of subcutaneous edema in DM (see Supplementary Material for references). In these cases, edema occurred in any extremity during the active phase of the disease and investigative studies typically ruled-out other causes of edema. Here, we found that subcutaneous edema was present in more than one third of anti-NXP-2 positive DM subjects but in less than one fifth of those who were anti-NXP-2-negative. In no case was another etiology such as thromboembolism, cardiac disease, or renal disease responsible for the edema. Rather, the edema typically occurred during the active phase of the disease, with resolution following administration of immunosuppressive therapy. Interestingly, we found that subcutaneous edema in both anti-NXP-2-positive and -negative DM subjects was associated with increased weakness and a muscle biopsy characterized by necrosis without primary inflammation. While the latter observation raises the possibility that edema may be associated with myofiber necrosis, edema has not been reported in patients with necrotizing muscle biopsies such as those with anti-HMG-CoA reductase autoantibodies. Nonetheless, the temporal association and improvement with immunosuppressive agents suggests that subcutaneous edema may be a direct manifestation of DM.

As originally reported (5) the current study confirms that calcinosis is associated with anti-NXP-2 autoantibodies. However, there was no association between muscle disease severity and the presence of calcinosis. Indeed, some patients developed progressive calcinosis long after the muscle disease had been well controlled.

Here, we demonstrate conclusively that anti-NXP-2 positive DM patients have an increased risk for malignancy compared to the general population. Specifically, our cohort of anti-NXP-2 patients included five with cancer within three years of the diagnosis of DM when less than two would be expected when controlling for age, and gender. As expected, we did not detect a statistically significant difference in the rates of cancer between DM patients with and without anti-NXP-2 autoantibodies, most likely because the latter group includes large numbers of anti-TIF-1γ-positive subjects who also have an increased risk of cancer.

One limitation of this study is the lack of reliable measurements of skin disease activity in our cohort of DM patients. This limitation notwithstanding, the current study shows that adult DM patients with anti-NXP2 autoantibodies have a unique clinical phenotype characterized by more severe weakness, a high prevalence of subcutaneous edema, and an increased risk of cancer which may justify more extensive testing for occult malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was supported in part by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH). LC-S and the Myositis Research Database are supported by the The Huayi and Siuling Zhang Discovery Fund. The Johns Hopkins Rheumatic Disease Research Core Center, where the NXP2 IVTT IP assays were performed, is supported by NIH grant P30-AR-053503. IPF is supported by a Fellowship from the Myositis Association.

References

1. Oddis CV, Fertig N, Goel A, Espada G, Confalone Gregorian M, Maldonado Cocco MA. Clinical and serological characterisation of the anti-MJ antibody in childhood myositis. Arthritis and Rheumatism. 1997; 40(S139)
2. Ichimura Y, Matsushita T, Hamaguchi Y, Kaji K, Hasegawa M, Tanino Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. Annals of the Rheumatic Diseases. 2012; 71(5):710–3. [PubMed: 22258483]
3. Betteridge Z, Gunawardena H, Chinoy H, Vencovsky J, Allard S, Gordon P. Autoantibodies to the P140 Autoantigen NXP-2 in Adult Dermatomyositis. Arthritis & rheumatology (Hoboken, NJ). 2009; 60(S):815.
4. Ceribelli A, Fredi M, Taraborelli M, Cavazzana I, Franceschini F, Quinzanini M, et al. Anti-MJ/NXP-2 autoantibody specificity in a cohort of adult Italian patients with polymyositis/dermatomyositis. Arthritis research & therapy. 2012; 14(2):R97. [PubMed: 22546500]
5. Gunawardena H, Wedderburn LR, Chinoy H, Betteridge ZE, North J, Ollier WE, et al. Autoantibodies to a 140-kd protein in juvenile dermatomyositis are associated with calcinosis. Arthritis and Rheumatism. 2009; 60(6):1807–14. [PubMed: 19479859]
6. Tansley SL, Betteridge ZE, Shaddick G, Gunawardena H, Arnold K, Wedderburn LR, et al. Calcinosis in juvenile dermatomyositis is influenced by both anti-NXP2 autoantibody status and age at disease onset. Rheumatology (Oxford, England). 2014; 53(12):2204–8.
7. Valenzuela A, Chung L, Casciola-Rosen L, Fiorentino D. Identification of clinical features and autoantibodies associated with calcinosis in dermatomyositis. JAMA dermatology. 2014; 150(7): 724–9. [PubMed: 24869801]
8. Fiorentino DF, Chung LS, Christopher-Stine L, Zaba L, Li S, Mammen AL, et al. Most Patients With Cancer-Associated Dermatomyositis Have Antibodies to Nuclear Matrix Protein NXP-2 or Transcription Intermediary Factor 1gamma. Arthritis and Rheumatism. 2013; 65(11):2954–62. [PubMed: 24037894]
9. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). The New England journal of medicine. 1975; 292(7):344–7. [PubMed: 1090839]
10. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis (dermatomyositis sine myositis). Presentation of six new cases and review of the literature. Journal of the American Academy of Dermatology. 1991; 24(6 Pt 1):959–66. [PubMed: 1869684]
11. Hoogendijk JE, Amato AA, Lecky BR, Choy EH, Lundberg IE, Rose MR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, The Netherlands. Neuromuscular disorders : NMD. 2004; 14(5):337–45. [PubMed: 15099594]
12. Werner JL, Christopher-Stine L, Ghazarian SR, Pak KS, Kus JE, Daya NR, et al. Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Arthritis and Rheumatism. 2012; 64(12):4087–93. [PubMed: 22933019]
13. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international

multidisciplinary classification of the idiopathic interstitial pneumonias. American journal of respiratory and critical care medicine. 2013; 188(6):733–48. [PubMed: 24032382]

14. Pinal-Fernandez I, Casal-Dominguez M, Carrino JA, Lahouti AH, Basharat P, Albayda J, et al. Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. Ann Rheum Dis. 2016
15. Pinal-Fernandez I, Casciola-Rosen L, Christopher-Stine L, Corse A, Mammen A. The prevalence of individual histopathologic features varies according to autoantibody status in muscle biopsies from dermatomyositis patients. Journal of Rheumatology. 2015

BULLET POINTS

- Dermatomyositis patients with anti-NXP2 autoantibodies have more myalgias, more severe weakness, and an increased prevalence of dysphagia than dermatomyositis patients without these autoantibodies.
- Subcutaneous edema and calcinosis are more prevalent in dermatomyositis patients with anti-NXP-2 autoantibodies compared to dermatomyositis patients who do not have these autoantibodies.
- Anti-NXP-2 positive patients have an increased risk of cancer compared to age-and sex-matched subjects in the general population.

Table 1

General features of DM patients with and without NXP-2 autoantibodies.

	Anti-NXP2 + (n=56)	Anti-NXP2 - (n=179)	p-value
Female	71% (40)	73% (130)	0.9
Age of onset	46.8 (17.7)	44.7 (14.8)	0.4
Time from the onset (years)	2.6 (4.6)	3.4 (4.8)	0.3
Race			
White	77% (43)	75% (135)	0.8
Black	9% (5)	13% (24)	0.4
Other races	14% (8)	11% (20)	0.5

*
<0.05;

**
<0.01;

***
<0.001

Continuous variables are expressed as mean (standard deviation [SD]) and bivariate variables as percentage (number). Logistic regression was used to compare bivariate variables and continuous variables were compared using linear regression.

Table 2

Comparison of weakness prevalence in DM patients with and without anti-NXP-2 autoantibodies by muscle group.

	Anti-NXP2+	Anti-NXP2-	Univariate p-value	p-value adjusted for time from onset
Neck	48% (25)	23% (35)	< 0.001 ***	< 0.001 ***
Upper proximal	65% (36)	53% (89)	0.10	0.07
Upper distal	35% (18)	20% (30)	0.03 *	0.02 *
Lower proximal	74% (37)	62% (97)	0.1	0.1
Lower distal	25% (13)	8% (13)	0.002 **	< 0.001 ***

* <0.05;

** <0.01;

*** <0.001

Muscle strength is expressed as percentage of patients with weakness (MRC strength less than 5) (raw number). The two groups of patients are compared using logistic regression. More than 80% of the patients had comprehensive manual muscle strength about all the muscles included in the study, patients with missing values in any of the muscles of the abovementioned muscle groups were excluded from this analysis.

Table 3

Clinical features of the patients depending on the anti-NXP2 status.

	Anti-NXP2 + (n=56)	Anti-NXP2 - (n=179)	Univariate p-value	p-value adjusted for time from onset
Edema	36% (20)	19% (34)	0.01 *	0.01 *
Dysphagia	62% (35)	35% (63)	< 0.001 ***	< 0.001 ***
Myalgia	46% (26)	25% (44)	0.002 **	0.002 **
ILD	7% (4)	28% (51)	0.003 **	0.002 **
Calcinosis	30% (17)	17% (31)	0.04 *	0.02 *
Cancer	9% (5)	8% (14)	0.8	0.9
Laboratory values				
CK value	108 (49-447)	135 (62-662)	0.3	0.7
ALD value	10.8 (8.5)	19.6 (55.4)	0.3	0.3
ESR value	35.2 (31.4)	23.2 (21.9)	0.009 **	0.02 *
CRP value	1.3 (1.5)	1.1 (3.0)	0.8	0.9
FVC(%)	89.2 (20.6)	85.0 (24.2)	0.4	0.5

*<0.05;

**<0.01;

***<0.001

^Patients presenting calcinosis at any time point during follow-up, the p-value for calcinosis has been adjusted for time to the last visit instead of time from onset.

CK:creatine kinase; ALD: aldolase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; FVC(%) percentage of forced vital capacity

CK is expressed as median, Q1 and Q3 and transformed through a base-10 logarithm for the regression analysis. The rest of the continuous variables are expressed as mean (standard deviation [SD]) and bivariate variables as percentage (number). Logistic regression was used to compare bivariate variables and continuous variables were compared using linear regression. All clinical features were available for each patient with the exception of CK (which was available in >85% of patients in each group) and ALD, ESR, CRP, and FVC(%) values (which were available for more than 50% of the patients in each group).