Serum interleukin-17A level is associated with disease activity of adult patients with dermatomyositis and polymyositis

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Abstract

Objective

To assess serum interleukin (IL)-17A levels in patients with dermatomyositis (DM) and polymyositis (PM) and correlate them with the demographic, clinical, laboratory and therapeutic data of these diseases.

Methods

This was a cross-sectional, single-centre study that included defined DM and PM patients who were age-, gender- and ethnicity-matched to healthy individuals. Serum IL-17A analysis, as well as analysis for other cytokines (IL-6, TNFα and IFNγ), was performed by multiplex immunoassay. The disease status parameters were based on the International Myositis Assessment and Clinical Studies Group (IMACS) set scores.

Results

Eighty DM, 32 PM patients and 104 healthy individuals were enrolled. Mean age of patients with DM and PM was 46.0 and 47.7, respectively, with a predominance of women and white ethnicity in both groups. Overall, clinical, laboratory, therapeutic, and current disease status were similar among patients with DM and PM. Median serum IL-17A level was higher in patients with PM and DM than the control group (0.73 vs. 0.49 vs. 0.35 pg/mL, respectively; $p<0.050$) and higher in PM when compared to DM ($p<0.001$). In DM, serum IL-17A levels were associated with cumulative cutaneous lesions, IMACS parameters, and serum IL-6 and IFNγ levels. In PM, serum IL-17A levels correlated with patients' current age, IMACS parameters and serum TNFα and IFNγ levels.

Conclusion

Serum IL-17A levels are not only increased, but also associated with disease activity in patients with DM and PM. Our data strongly suggest that IL-17A may be a biomarker of disease activity for these systemic autoimmune myopathies.

Key words

cytokines, dermatomyositis, interleukins, myositis, polymyositis

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Introduction

Dermatomyositis (DM) and polymyositis (PM) are systemic autoimmune myopathies (SAM) that affect primarily skeletal striated musculatures. They are characterised clinically by progressive, symmetrical and predominantly proximal muscular weakness of the limbs (1-4). In DM, there are also classical cutaneous lesions, such as heliotrope rash and Gottron's papules (1, 2).

Interleukin (IL)-17 is a proinflammatory cytokine synthesised mainly by T helper type 17 (Th17) cells and acting primarily on connective, epithelial and endothelial tissue cells (5-9). Th17 lineage can still be differentiated by the action/signalling of other cytokines to enhance the immune response (5, 6), and may promote the production of other proinflammatory cytokines, such as tumour necrosis factor (TNF)α, interferon (IFN) γ and IL-6 (7-9). In addition, several studies have shown the participation of IL-17 in the induction and maintenance of the systemic inflammatory process of several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and Sjögren's syndrome (7-13).

Despite the scarcity of studies available in literature, the participation of IL-17 has also been described in SAM (14-23). In the histological aspect, Yin *et al*. (24) observed a high IL-17 production by the inflammatory cells present in the muscle tissues of SAM patients. Page *et al*. (22) noted increased IL-17 and a high IFNγ expression in muscle tissues. Fujiyama *et al*. (21) showed increased IL-17A in cutaneous lesions of patients with DM.

From the systemic point of view, Notarnicola *et al*. (12) examined a small sample of patients with SAM (10 DM, 14 PM e 7 anti-synthetase syndrome), and found an increase in serum IL-17 concentration, as well as a correlation with disease duration, serum IL-15 concentration and one of the parameters of disease activity (muscle strength assessed by the Manual Muscle Testing - 8: MMT-8). Shen *et al*. (16) observed an increase in serum IL-17 in DM and PM, but only in the initial phase of these diseases (disease duration <1 year), suggesting that this cytokine is particularly involved in the establishment and development of these diseases. However, these authors (16) did not correlate the level of serum IL-17 concentration with any parameters of SAM activity.

These few available data in literature reinforce the relevance of IL-17 in SAM. Therefore, the aims of the present study were: to assess serum IL-17A level in a representative sample of adult patients with defined DM and PM and to correlate this IL with demographic, clinical, laboratory, therapeutic and disease status parameters of DM and PM.

Materials and methods

It is a cross-sectional, single-centre study that included 112 consecutive patients with SAM (80 defined DM and 32 defined PM) according to the criteria of Bohan and Peter (1), Even being included before the current classification, they also fulfilled the new parameters of European League Against Rheumatism/American College of Rheumatology (2017 EULAR/ACR) classification criteria (25). Patients were evaluated in an outpatient clinic from 2012 to 2016. The study was approved by the local ethics committee and all participants signed the informed consent form. Patients exhibited immune-mediated necrotising myopathy (anti-SRP or anti-HMGCR positive autoantibodies), antisynthetase syndrome (anti-Jo-1, OJ, EJ, PL-7, PL-12 positive autoantibodies), clinically amiopathic DM, inclusion body myositis, overlap's syndrome, myopathies associated with neoplasia, and/or acute or chronic infections were excluded from the present study.

As a control group, 104 healthy volunteers, matched for age, gender and ethnicity were recruited during the same period.

Participants underwent a clinical evaluation that included a standardised interview and the following data were collected:

- Demographic: current age, gender and ethnicity
- Clinical and laboratory data: age at disease onset, duration of disease, cumulative clinical manifestations: articular (arthralgia or arthritis - non-erosive and non-deforming), pulmonary (defined as the presence of re-

ported dyspnea and altered computed tomography: incipient pneumonia, ground-glass lesion or basal fibrosis), (Gottron's sign/papules, heliotrope rash, ulcers, vasculitis, facial rash, "shawl" sign, "V-neck" sign, calcinosis), serum creatine phosphokinase (reference value 26–308 U/L), alanine aminotransferase (<31 U/L), aspartate aminotransferase (<31 U/L), lactic dehydrogenase (135–214 U/L), and aldolase (≤7.6 U/L) analysed by the automated kinetic method

- Evaluation of the patient's disease status through the application of questionnaires and scores established by the International Myositis Assessment & Clinical Studies Group (IMACS) set scores: visual analogue scale (VAS) performed by patient and physician, Health Assessment Questionnaire (HAQ), MMT-8, Myositis Disease Activity Assessment Visual Analogue Scale (MYOACT) and serum concentration of muscle enzymes (26-31)
- Drug treatment: immunosuppressive, immunomodulatory, immunobiological and glucocorticoid (current and cumulative doses in the last three months).

Cytokine analysis

For analysis of the serum concentration of IL-17A, IL-6, TNF-α and IFNγ, 10 mL of venous blood were collected from participants after a 12 - hour fast. The samples were immediately (<30 minutes) centrifuged at 3000 rpm for 10 minutes at 4°C. After processing, the serum was stored in a freezer at -80°C. Serum concentrations of the cytokines were determined from a microspheres-containing immunoassay for multiple protein analysis using the R&D Magnetic Luminex Screening Assay kit (R&D Systems, IncMinneapolis, MN, USA), carried out according to the manufacturer's specifications. Quantification of the cytokines was done with the equipment (Luminex 200TM, Luminex®, MiraiBio, CA), using 25 µL of serum of each participant. Sample concentrations were estimated from the standard curve using MILLIPLEX Analyst software and cytokine levels were expressed as total amount per site.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normal distribution of each continuous parameter. Data were expressed as mean ± standard deviation for continuous variables or as frequency (%) for categorical variables. Median (interquartile 25%–75%) was calculated for continuous variables with non-normal distribution. Comparisons between patient parameters and controls were performed using the Student's *t*-test or Mann-Whitney test for continuous variables, and the chi-square test or Fisher's exact test were used to evaluate categorical variables. The correlation (*rho*) between the parameters was analysed by Spearman correlation. We considered weak values between 0 and ±0.333 weak correlations; moderate between ±0.333 and ±0.666; and strong between ±0.666 and ±1.000. In addition, *p*-values <0.050 were considered statistically significant. All analyses were performed with the statistical software SPSS 15.0 (Chicago, IL, USA).

Results

We evaluated 80 patients with defined DM and 32 PM, who were compared with 104 healthy individuals. Mean age was 46.0, 47.7 and 43.7 years in the DM, PM and control groups, with a predominance of female gender and white ethnicity (Table I).

Median duration between diagnosis and symptoms' onset was 6 months for both groups (DM and PM) and median duration of the disease was 3 and 5 years for patients with DM and PM, respectively. Regarding cumulative clinical and laboratory characteristics, only skin changes were observed in patients with DM in the following descending order: Gottron's sign/papules, heliotrope rash, facial rash, "V-neck" sign, vasculitis, "shawl" sign and ulcers. The frequency of joint and pulmonary involvement as well as the initial serum creatine phosphokinase concentration were similar in patients with DM and PM ($p>0.050$). Regarding drug treatment, at the time of clinical and laboratory data collection, about half of the patients were using prednisone with a median dose of 5 mg/day and cumulative dose in the last 3 months of 450 and 250 mg in patients with DM and PM, respectively. In addition, approximately 60% of the patients were using immunosuppressive drugs.

Table II shows the status of patients with DM and PM, based on the criteria used to assess disease activity, in which median values of patient and physician VAS, HAQ, MYOACT and serum concentration of muscle enzymes were comparable between patients with DM and PM, except for the lower value of MMT-8 and higher serum creatine phosphokinase levels in patients with PM when compared to DM ($p<0.050$).

Serum IL-17A concentrations were increased in patients with DM and PM when compared to the control group ($p<0.050$) (Table II). In addition, this IL was higher in PM than in DM ($p=0.001$). Regarding other cytokines, serum concentrations of IL-6, IFNγ and TNF-α were increased in patients with DM compared to the control group, whereas in PM, only IL-6 and TNF-α were elevated. Furthermore, serum IFNγ and TNF-α concentrations were higher in patients with DM, compared to PM ($p<0.001$).

Additionally, a correlation analysis between serum concentrations of IL-17A was performed on all parameters (demographic, clinical, laboratory, therapeutic and disease status) and is presented in Tables I and II.

All correlations between IL-17A and the various parameters analysed are presented in Table III. Of note, the serum IL-17A concentrations did not correlated with therapeutic parameters.

In patients with PM, the current age of the patients, MMT-8 and TNF-α correlated inversely with the serum concentration of IL-17A. The other parameters of the disease activity, *i.e.* patient and physical VAS, HAQ, MYOACT (VAS constitutional symptoms), creatine phosphokinase, and IFNγ correlated positively with serum IL-17A. In patients with DM, only MMT-8 correlated inversely with the serum concentration of IL-17A. The other parameters: VAS patient and physician, HAQ, MYOACT (VAS constitutional and cutaneous symptoms), cumulative clinical manifestations (facial rash, "V-neck" sign, "shawl" sign), muscle enzymes, and cytokines (IL-6 and IFNγ) correlat-

Table I. Demographic data of dermatomyositis, polymyositis and healthy subjects and cumulative characteristics and general therapeutic treatment of patients with dermatomyositis and polymyositis.

Parameters	DM (n=80)	PM (n=32)	Control (n=104)	*p*-value		
				DM *vs.* Control	PM *vs.* Control	DM *vs.* PM
Current age (years)	46.0 ± 13.9	47.7 ± 14.3	43.7 ± 11.6	0.397	0.475	0.817
Disease time (years)	3 (0-6)	5 (2-10)	-	-	-	0.019
Time: symptoms (months) - diagnosis	6 (3-10)	6 (3-12)	-	-	-	0.337
Female gender	57 (71.2)	24 (75.0)	76 (73.1)	0.868	1.000	0.817
White ethnicity	55 (68.8)	17 (53.1)	58 (55.8)	0.868	0.475	0.127
Cumulative features						
Gottron's papules / sign	76 (95.0)	0	-	-	-	-
Heliotrope rash	69 (86.3)	0	-	-	-	-
Facial rash	54 (67.5)	0	-	-	-	-
"V-neck" sign	28 (35.0)	0	-	-	-	-
Vasculitis	23 (28.8)	0	-	-	-	-
"Shawl" sign	0	-	-	-	-	
Ulcers	12 (15.0)	0	-	-	-	-
Calcinosis	0	0	-	-	-	-
Joint involvement	28 (35.0)	11 (34.4)	-	-	-	1.000
Pulmonary involvement	26 (32.5)	8 (25.0)	-	-	-	0.501
Initial creatine phosphokinase (U/L)	1297 (252-9030)	1966 (967-8966)	-	-	-	0.303
Prednisone						
Current use	47 (58.8)	15 (46.9)	-	-	-	0.296
Current dose (mg/day)	5 (0-20)	5 (0-15)	-	-	-	0.383
Cumulative dose: last 3 months (mg)	450 (0-1800)	250 (0-1350)	-	-	-	0.384
Current immunosuppressive drugs *	47 (58.8)	19 (59.4)	-	-	-	1.000
One	32 (40.0)	16 (50.0)	-	-	-	0.400
Two	15 (18.8)	3 (9.4)	-	-	-	0.551

DM: dermatomyositis; PM: polymyositis.
Results expressed as mean ± standard deviation, median (interquartile 25th - 75th) or frequency (%).
*Azathioprine (2-3 mg/kg/day), cyclosporine (2.0-3.0 mg/kg/day), leflunomide 20 mg/day, methotrexate (15-25 mg/week), mycophenolate mofetil (2-3 g/day), rituximab [1 g, intravenous, at baseline and after one month (first cycle) repeating this regimen after six months], and/or intravenous human immunoglobulin (2 g/kg, 1x/day, two consecutive days).

Table II. Parameters of disease activity and serum concentration of cytokines in patients with DM, PM and healthy individuals.

Parameters	DM (n=80)	PM (n=32)	Control (n=104)	*p*-value		
				DM *vs.* .Control	PM *vs.* Control	DM *vs.* PM
Patient VAS (0-10 cm)	2.5 (0.0-6.0)	2.5 (1.0-6.0)	-	-	-	0.400
Physician VAS (0-10 cm)	2.0 (0.0-5.0)	2.0 (0.3-5.8)	-	-	-	0.676
HAQ (0.00-3.00)	0.29 (0.00-2.00)	0.79 (0.43-1.83)	-	-	-	0.214
MMT-8 (0-80)	80 (72-80)	74 (64-80)	-	-	-	0.048
MYOACT (0-60)	0.1 (0.0-1.3)	0.2 (0.0-0.5)	-	-	-	0.321
Creatine phosphokinase (U/L)	134 (79-352)	358 (120-567)	108 (85-144)	0.011	<0.001	0.027
Aldolase (U/L)	4.8 (4.0-6.4)	6.2 (3.6-8.4)	3.6 (2.9-4.4)	<0.001	<0.001	0.131
Lactic dehydrogenase (U/L)	417 (368-502)	467 (354-544)	340 (309-389)	<0.001	<0.001	0.475
Aspartate aminotransferase (U/L)	29 (19-41)	25 (16-20)	20 (16-23)	<0.001	<0.001	0.550
Alanine aminotransferase (U/L)	25 (16-39)	25 (20-42)	17 (14-22)	<0.001	<0.001	0.240
IL-17 (pg/mL)	0.49 (0.28-0.83)	0.73 (0.53-1.14)	0.35 (0.09-0.61)	0.003	<0.001	0.001
IL-6 (pg/mL)	1.24 (0.75-2.60)	1.83 (0.91-2.94)	0.71 (0.52-0.97)	<0.001	<0.001	0.438
IFNγ (pg/mL)	0.41 (0.25-0.74)	0.33 (0.33-0.90)	0.36 (0.22-0.73)	0.019	0.064	<0.001
TNF-α (pg/mL)	3.60 (2.51-5.96)	6.14 (3.83-8.60)	2.27 (1.57-5.83)	0.003	0.001	<0.001

DM: dermatomyositis; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; IFN: interferon; IL: interleukin; MMT: Manual Muscle Testing; MYOACT: Myositis Disease Activity Assessment VisualAnalogue Scales; PM: polymyositis; TNF: tumour necrosis factor.

ed positively with serum IL-17A levels. Figures 1 and 2 illustrate the correlationship between serum IL-17A level and disease activity parameters established by IMACS in PM and DM patients, respectively.

Discussion

In the present study, high serum IL-17A levels were observed in adult patients with DM and PM, and more in PM than DM. Moreover, IL-17A correlated with the disease activity parameters of these SAM, thus confirming the role of this cytokine in the development and maintenance of SAM.

A representative sample of patients with defined DM and PM was included in this study, even after the application of

Table III. Relationship between serum concentration of IL-17 and the different parameters analysed in the study.

	DM		PM	
	Rho	*p*-value	Rho	*p*-value
Current age	-0.121	0.285	-0.492	0.014
Disease time (years)	-0.030	0.791	-0.107	0.618
Time: symptoms (months) - diagnosis	-0.005	0.966	-0.182	0.394
Female gender	0.150	0.184	0.103	0.633
White ethnicity	-0.071	0.532	-0.012	0.955
Cumulative features				
Gottron's papules / sign	-0.098	0.389	-	-
Heliotrope rash	0.031	0.786	-	-
Facial rash	0.302	0.006	-	-
"V-neck" sign	0.262	0.019	-	-
Vasculitis	-0.085	0.454	-	-
"Shawl" sign	0.310	0.005	-	-
Ulcers	-.0.015	0.898	-	-
Calcinosis	-	-	-	-
Joint involvement	0.050	0.661	-0.219	0.305
Pulmonary involvement	-0.115	0.311	-0.154	0.472
Initial creatine phosphokinase (U/L)	-0.049	0.725	0.156	0.535
Prednisone				
Current use	0.169	0.134	-.0231	0.277
Current dose (mg/day)	0.122	0.280	0.013	0.953
Cumulative dose: last 3 months (mg)	0.179	0.111	0.092	0.669
Current immunosuppressive drugs *	-0.199	0.076	-0.080	0.711
One	-0.131	0.247	-0134	0.533
Two	-0.032	0.779	0.082	0.702
Disease status				
Patient VAS	0.327	0.003	0.606	0.002
Physician VAS	0.325	0.003	0.600	0.002
HAQ	0.229	0.041	0.537	0.007
MMT-8	-0.403	<0.001	-0.536	0.007
MYOACT	0.375	0.001	0.309	0.142
VAS (constitutional symptoms)	0.342	0.002	0.444	0.030
VAS (cutaneous)	0.342	0.002		-
VAS (skeletal)	0.137	0.225	0.038	0.861
VAS (gastrointestinal)	0.003	0.976	-	-
VAS (cardiac)	0.175	0.121	-	-
VAS (pulmonary)	0.108	0.342	-	-
Creatine phosphokinase	0.428	<0.001	0.440	0.036
Aldolase	0.390	0.001	0.296	0.160
Alanine aminotransferase	0.227	0.049	0.027	0.901
Aspartate aminotransferase	0.399	<0.001	-0.010	0.964
Lactic dehydrogenase	0.474	<0.001	0.127	0.553
IL-6	0.470	<0.001	0.292	0.166
IFNγ	0.669	<0.001	0.748	<0.001
TNF-α	0.122	0.280	-0.433	0.035

DM: dermatomyositis; EVA: visual analogue scale; HAQ: Health Assessment Questionnaire; IFN: interferon; IL: interleukin; MMT: Manual Muscle Testing; MYOACT: Myositis Disease Activity Assessment Visual Analogue Scales; PM: polymyositis; *Rho*: Spearman correlation; TNF: tumour necrosis factor; VAS: visual analogue scale.
*Azathioprine (2-3 mg/kg/day), cyclosporine (2.0-3.0 mg/kg/day), leflunomide 20 mg/day, methotrexate (15-25 mg/week), mycophenolate mofetil (2-3 g/day), rituximab [1 g, intravenous, at baseline and after one month (first cycle) repeating this regimen after six months], and/or intravenous human immunoglobulin (2 g/kg, 1x/day, two consecutive days).

strict exclusion criteria for diseases considered rare. In addition, by considering that demographic factors may interfere in the interpretation of the results (32), patients were also matched by gender, age and ethnicity to the control group.

Our patients were comparable in regard to demographic, clinical, laboratory, and therapeutic data. Nevertheless, patients with PM presented longer disease times and more representative muscle weakness, as well as higher concentration levels of muscle enzymes at the disease's onset.

IL-17 is a proinflammatory cytokine and is implicated in the pathophysiology of various systemic autoimmune diseases (7-24), including SAM (14-24). In fact, a high IL-17 expression has been observed in cutaneous lesions (21) and muscle tissue samples (17, 22, 24) of patients with SAM, reinforcing the possible involvement of Th17 in the pathogenesis of these diseases. On the other hand, Giris *et al*. (20) did not identify an increase in IL-17 in muscle tissues of patients with DM, but of other cytokines, such as IFN and IL-4, which also correlated the degree of patient's muscle weakness.

Reinforcing our data, other studies have shown a high serum IL-17 level in patients with SAM (14, 16). For instance, Shen *et al*. (16) observed elevated serum IL-17 levels in early DM and PM (disease duration <1 year) when compared to the control group, suggesting that this IL can be involved in the physiopathogenesis of these diseases. However, these authors (16) did not specifically evaluate disease activity parameters or give details of drug treatments at the time of serum IL-17 analysis. This last aspect is relevant, because it is important to consider if patients are at disease onset or not, in immunosuppressive treatment or not, and in an active phase or not, because all these situations may influence IL-17A levels.

Notarnicola *et al*. (14) also observed an increase in serum IL-17 concentration in patients with SAM. However, these authors (14) analysed the pool serum IL-17 of relatively small sample of patients with SAM (PM, DM and antisynthetase syndrome). Moreover, these authors (14) noted that IL-17 was associated with only one of the IMACS (MMT-8) set scores.

Possible interaction between IL-17 and other proinflammatory cytokines (*i.e*. TNF-α, IFNγ and IL-6) has been demonstrated in the literature (7-9). Specifically, in the present study, there was a positive correlation between serum IL-17A and IFNγ in patients with DM and PM. Serum IL-17A correlated also positively with IL-6 in DM, and negatively with TNFα in PM.

Several studies have shown the involvement of IFNγ in SAM pathophysiology (peripheral blood, muscular and cutaneous tissues), possibly modu-

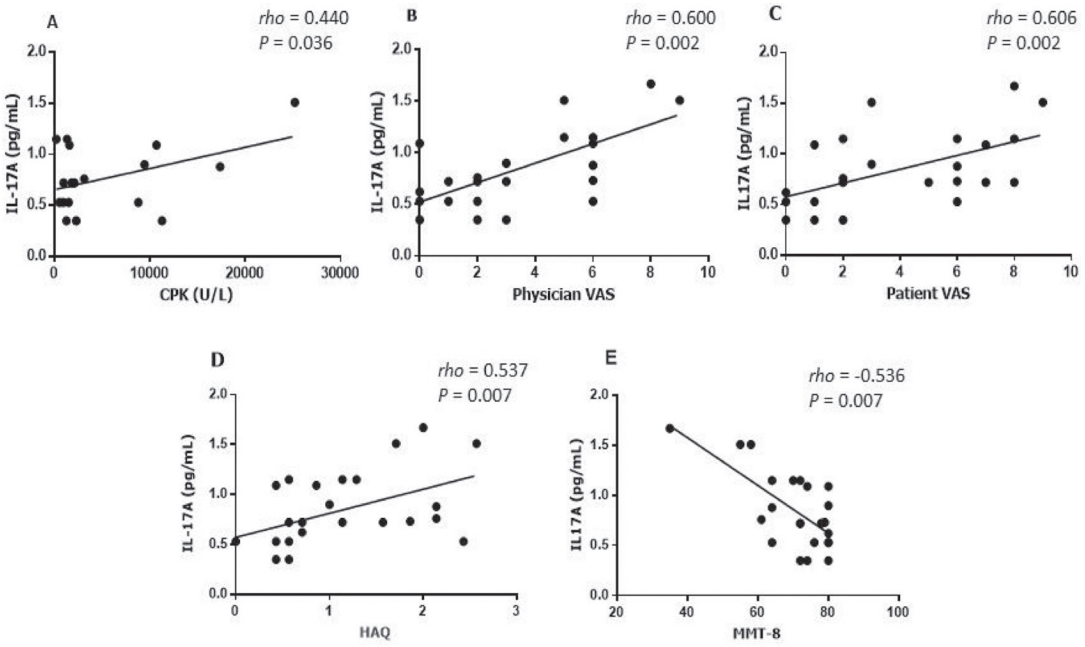

Fig. 1. The Spearman correlationship between serum IL-17A level and disease activity parameters established by IMACS in polymyositis patients.

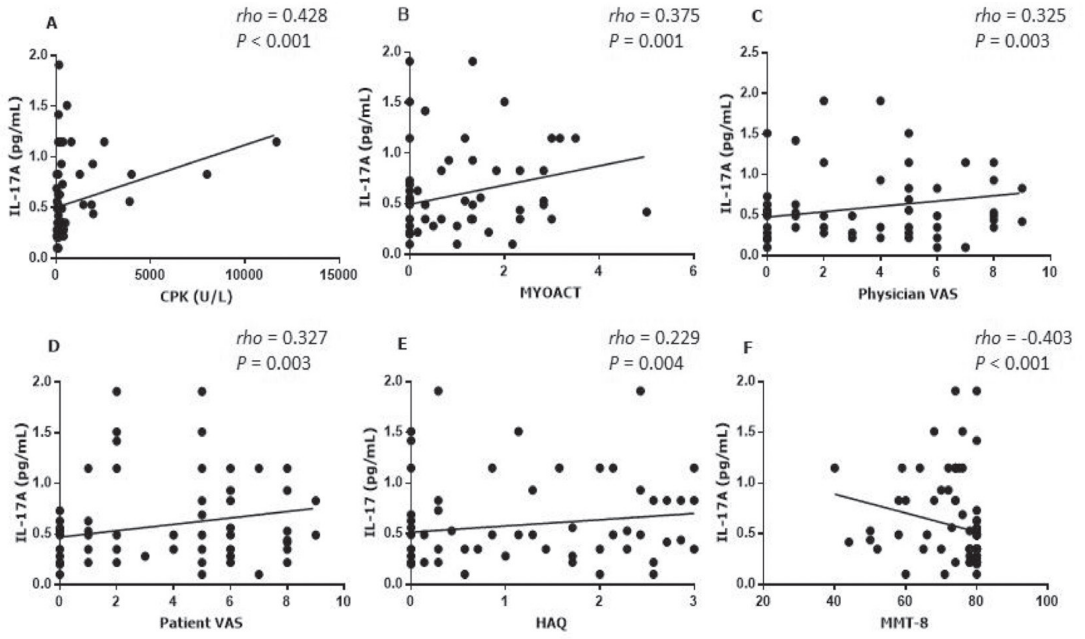

Fig. 2. The Spearman correlationship between serum IL-17A level and disease activity parameters established by IMACS in dermatomyositis patients.

lating Th17 cells (types 1 and 2) (20, 33-35), which lead to the production of IL-17. As previously mentioned, IL-17 may lead to the production of other proinflammatory cytokines, including IL-6, TNF-α, and IFNγ itself and, consequently, may perpetuate the mechanism of pathophysiology (7-9).

IL-6 is a pleiotrophic proinflammatory cytokine that acts on humoral and cellular immunity (36). In the present study, serum IL-6 levels were increased in patients with DM and PM when compared to healthy individuals, corroborating data available in the literature (37). However, serum IL-6 correlated positively with serum IL-17 levels only in patients with DM.

TNF-α, another proinflammatory cytokine analysed in the present study, was increased in patients with DM and PM, as also shown in the literature (37). However, this protein inversely correlated with the serum IL-17 levels of PM patients. TNF-α acts synergistically with IL-17, regulating inflammatory gene expression (13, 38). This population of Th producing strain is characterised by the co-expression of IL-17 and TNF-α (13) and the occurrence of this subclass of cytokines seems to depend on the stage and location of the disease (38).

The influence of drug treatment on serum IL-17 level should be considered, since the long-term drug treatment has some effect, decreasing the levels of the cytokines studied. However, in the present study, serum IL-17A concentration levels remained high and there was no statistical significance between the increased values in patients treated or at least not at the time of IL-17 analysis.

Therefore, the study also presented a view of the IL-17A response in relation to the drug treatment for SAM, which is relevant because it demonstrated that the action of the drugs at that moment (cross-section) did not interfere in the serum IL-17A profile.

In summary, the study addressed the performance of an important protein in an expressive sampling of rare diseases such as DM and PM, demonstrated the elevation of IL-17A in the serum of patients compared to healthy individuals, evidenced the involvement of this IL in SAM. These findings reinforce the profile of IL-17A as an essential regulator of the inflammatory response and prove the relevance of this potential biomarker for DM and PM activity and therefore a possible therapeutic target.

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