ORIGINAL ARTICLE

Complement Activation Products (C3a and C5b-9) as Markers of Activity of Dermatomyositis. Comparison With Tradicional Laboratory Markers

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Abstract. *Introduction.* Dermatomyositis (DM) is an autoimmune disease included in the group of idiopathic inflammatory myopathies. Markers of disease activity are needed for clinical control in order to facilitate adjustment of immunomodulatory therapy. We analyzed the relationship between complement activation products (CAP) and the activity of dermatomyositis and its usefulness in the follow-up of the disease and the prediction of recrudescences related to usual biochemical parameters.

Material and methods. We studied 16 patients with DM that were followed periodically. In each appointment the degree of cutaneous and muscular activity was assessed and such disease activity was correlated with plasma levels of C3a and C5b-9, measured by ELISA.

Results. Though we obtained certain correlation between disease activity and plasma levels of C3a and C5b-9, the strength of such correlation was not superior to that obtained by usual biochemical markers. C3a was shown to be the most sensitive marker (100%) with a sufficient specificity (83.3%) in the capability to predict recrudescences.

Conclusions. C3a and, to a lesser extent C5b-9, would be useful in the identification of patients with especially active DM as well as in predicting disease recrudescences. Nevertheless they are not superior to the rest of biochemical markers as indicators of current activity.

Key words: dermatomyositis, activity, recrudescence, complement system, C3a, C5b-9, creatine phosphokinase.

PRODUCTOS DE ACTIVACIÓN DEL COMPLEMENTO (C3A Y C5B-9) COMO MARCADORES DE ACTIVIDAD DE LA DERMATOMIOSITIS. COMPARACIÓN CON PARÁMETROS BIOQUÍMICOS TRADICIONALES

Resumen. *Introducción.* La dermatomiositis (DM) es una enfermedad de origen autoinmune, incluida en el grupo de las miopatías inflamatorias idiopáticas. En el control clínico de este proceso se precisan marcadores que permitan determinar el grado de actividad de la enfermedad, facilitando así el ajuste a la terapia inmunomoduladora. Se analiza la relación entre los productos de activación del complemento (PAC) y la actividad de la DM y su utilidad en el seguimiento de la enfermedad y en la predicción de las reagudizaciones en relación a los parámetros bioquímicos habituales.

Material y métodos. Se estudiaron 16 pacientes con DM, que fueron seguidos periódicamente. En cada revisión se estableció el grado de actividad cutánea y muscular del proceso, y se correlacionó dicha actividad con los niveles plasmáticos de C3a y C5b-9, determinados mediante técnica de ELISA.

Resultados. Si bien se obtuvo cierta correlación entre la actividad del proceso y los niveles plasmáticos de C3a y C5b-9, la intensidad de dicha correlación no superó la obtenida por los marcadores bioquímicos tradicionales. En la capacidad de predicción de reagudizaciones, C3a se mostró como el marcador más sensible (100 %), con una especificidad suficiente (83,3 %).

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Manuscript accepted for publication April 3, 2007.

This study was financed by grant FIS: 99/0177.

Conclusiones. C3a y en menor medida C5b-9 serían de utilidad en la identificación de pacientes con DM especialmente activas, así como en la predicción de reagudizaciones del proceso. Sin embargo, no tienen una utilidad superior al resto de marcadores bioquímicos como marcadores de actividad actual.

Palabras clave: dermatomiositis, actividad, reagudización, sistema del complemento, C3a, C5b-9, creatinfosfoquinasa.

Introduction

Dermatomyositis is an autoimmune disease within the idiopathic inflammatory myopathy group.[1-4] The main aim of treatment is to prevent possible complications arising from visceral involvement or from progression or recrudescence of the disease process, and to minimize possible treatment-induced iatrogenic effects. In recent years, attempts have been made to determine those parameters that would help to identify especially aggressive forms of the disease and to assess disease course once treatment has been initiated. The diagnostic parameters (muscle strength, muscle enzymes, histological findings, electromyographic findings) are not sufficiently sensitive or specific to assess response to treatment.[5-14] Thus, different authors have studied the association between disease activity and the factors involved in the pathogenesis of the disease process, such as variables relating to the degree of muscle damage,[15-26] markers of endothelial damage,[9,27-31] immunological variables,[32-46] cytokines and adhesion molecules,[35,47-51] and others.[52-55]

Even though many of these variables have proven useful as markers of clinical activity, none have displayed a level of correlation sufficient to replace the biochemical markers traditionally used.

Histopathological findings suggest that the muscle damage typical to dermatomyositis is the result of microangiopathy mediated by complement.[56-62] Deposits of the membrane attack complex C5b-9 have been observed in the muscle microvasculature of a significant percentage of adolescents and adults with DM at very early stages of the disease,[64-66] and their intensity has been associated with how aggressive the process is at the local level.

Thus, measuring the degree of complement activation might be a possible approach to determine the level of disease activity. Although periodic and serial measurement of variables such as hemolytic activity (CH50) or serum levels of the different components can be useful in establishing the dynamic state of the system, analysis of complement activation products (CAP) can be used as a measure of the catabolic state and, thus, is a more precise measure of its level of activation. Although the involvement of the complement system in the pathogenesis of dermatomyositis has been clearly established, to date, few studies have focused on the analysis of CAP levels in patients with this disease.[67]

We investigated the association between the level of activation of the complement system—analyzed based on plasma levels of 2 CAPs (C3a-desArg and SC5b-9)—and the clinical activity of dermatomyositis. Given the involvement of the complement system in the initial phases of the disease, we assessed the usefulness of the serial measurement of these variables in predicting recrudescence of the disease.

Materials and Methods

Patients

The study included 16 patients (10 women; 6 men; mean age, 53 years; range, 24-82 years) who fulfilled the Bohan and Peter[7-8] diagnostic criteria for dermatomyositis or the Sontheimer[68] criteria for amyopathic dermatomyositis. Patients were recruited from the Dermatology, Internal Medicine, and Autoimmune and Systemic Disease departments of Hospital Clinic de Barcelona and the Dermatology Department of Hospital General de Cataluña. The patients were classified as either *a)* active disease, *b)* nonactive disease at baseline, or *c)* recrudescence. The study period was 21 months (April 1998 to January 2001). Plasma and serum samples were taken from each person at each visit (15 mL blood).

Control Group

Plasma samples from 34 healthy individuals (24 women; 10 men; mean age, 45 years; range, 19-65 years) who donated blood at the blood bank of the Hospital Clínic de Barcelona were used as controls.

Clinical Assessment

The patients were assessed every 2 months by the same researcher, who was not involved in the normal health care of the patient.[9,34,69,70] Care was provided simultaneously and

independently in the appropriate department. The researcher did not participate in therapeutic decisions and was not aware of the results of other examinations. The extent of the disease was quantified in 18 proximal muscle groups at each visit, using assessment scales designed for this purpose, and according to previously defined criteria.[71]

As there were no predesigned scales for quantifying skin lesions due to dermatomyositis, we created our own assessment scale (Table 1). Total disease activity was calculated by summing skin and muscle scores.

We also assessed the presence of myalgia, signs and symptoms of visceral involvement, and association with vasculitis. Information was collected on UV radiation exposure, the development of disease (infectious or inflammatory) between visits, and the treatment required for management of dermatomyositis.

Patient Classification and Diagnosis of Recrudescences at Each Visit

1. Active dermatomyositis was diagnosed if the following criteria were met: *a)* the total activity score was higher than 2, and *b)* treatment was required.

2. If the above criteria were not met, inactive dermatomyositis was diagnosed.

3. Recrudescence was diagnosed when the following conditions were met: *a)* total activity scores were increased in relation to previous assessment, and *b)* it was necessary to increase the doses of normal medication, add another immunomodulatory drug, and/or admit the patient to hospital due to this increase in clinical activity.

Traditional Laboratory Markers of Activity

Traditional biochemical variables were analyzed at each visit (erythrocyte sedimentation rate [ESR], complete blood count, creatinine, creatine phosphokinase [CPK], aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], lactate dehydrogenase [LDH], aldolase, C3 and C4) in the laboratory of Hospital Clínic de Barcelona.

Measurement of Plasma CAP Levels

Plasma SC5b-9 and C3a-desArg levels were measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits (C3a-desArg ELISA kit, SC5b-9 EIA kit; Quidel, San Diego, USA) and a LABOTECH automated ELISA reader (IFCI Clone Systems, Casalecchio Di Reno, Italy). All samples (patients and control group) were simultaneously analyzed in duplicate and on 2 different occasions without the patient's clinical status and identity being known. The final value of the levels for each visit was obtained by calculating the mean of the 4 values obtained.

Table 1. Skin Score Scale[a]

Skin Lesion	*Score*
Macular erythema	% body area affected/10
Heliotrope rash	Not present: 0 Present: 1 Associated with palpebral edema: 2
Gottron sign or papules	Not present: 0 <5 elements: 1 5 to 10 elements: 2 >10 elements: 3
Erythema or cuticular dystrophy	Not present: 0 <5 fingers affected: 1 5 to 10 fingers affected: 2 >10 fingers/toes affected: 3
Other cutaneous lesions: flagellate erythema, palmar hyperkeratosis, oral aphthous ulcers, skin erosions, blisters, panniculitis, livedo reticularis, alopecia	1 point for each lesion

[a]Two measurements were taken at each visit (before and after the clinical interview). The definitive score is provided by the mean of the 2 measurements.

Statistical Analysis

Comparison of Mean Plasma Levels in Active and Inactive Dermatomyositis and in Control Subjects

A linear mixed model was used in which the values of the variables (C3a-desArg and SC5b-9) were logarithmically transformed due to their marked asymmetric distribution and the presence of extreme values.

Assessment of the Correlation between CAP Levels and Other Markers of Biochemical Activity and Clinical Disease Activity Scores

The Spearman rank correlation coefficient was calculated for the correlation between clinical scores and analytical variables from patients with data available from more than 3 visits. A single Spearman rank correlation was also calculated based on data from all patients.

Usefulness of Specific and/or Serial Measurements of CAP to Predict Recrudescence of the Disease

Recrudescence was identified using the clinical criteria previously defined. To assess the usefulness of specific

measurements of C3a-desArg and SC5b-9 for predicting recrudescence, analytical results were considered positive when, in the 4 months prior to the recrudescence, the values were above the 95th percentile of the normal range determined in the control group. In terms of the usefulness of serial measurements of the different analytical variables studied, tests were considered positive when there was more than 20% variation or there was a 50% increase or decrease in levels, if previous levels were in the normal range for those markers. All observed increases were considered positive in the case of CAP, given the absence of previous studies establishing the significance of prospective variations. We analyzed the sensitivity and specificity of these markers as predictors of recrudescence. Taking into account the low number of identified recrudescences, we did not carry out an inferential analysis (tests of statistical significance) of the predictive power of the different analytic markers of activity to predict clinical activity.

Results

The clinical characteristics of the patients are summarized in Table 2. The mean duration of the disease prior to the study was 15 months (range, 0-96 months). Mean time between visits was 2.7 months (range, 1.5-6 months). There was a total of 54 visits (105.5 patient-months) with a mean of 3.3 visits per patient (range, 1-7). The disease was considered active in 12 patients and inactive in 4 at the time of inclusion in the study. The disease status changed from active to inactive during follow-up in 4 patients.

Comparison of Plasma Levels of C3a-desArg and SC5b-9 in Patients with Active Dermatomyositis, Inactive Dermatomyositis, and Control Individuals

Table 3 shows the mean, median, and SD of C3a-desArg and SC5b-9 levels in the different groups (active dermatomyositis, inactive dermatomyositis, and control group). In the analysis performed with the natural logarithm for C3a-desArg, the estimations of the difference between means (95% confidence interval) were as follows: *a)* −0.7461 (−1.0283 to −0.4639) between control group and active dermatomyositis (P<.0001); and *b)* 0.5784 (0.1669-0.9899)between active and inactive dermatomyositis (P=.0066). No significant differences

Table 2. Patient Characteristics

Patient	*Sex*	*Age, y*	*Diagnosis*	*Active/Inactive Disease*	*Associated Diseases*	*Number of Visits*
1	F	58	DMc	Active	Autoimmune thyroiditis Sjögren syndrome	6
2	F	54	DMm	Inactive	Pulmonary adenocarcinoma	6
3	M	24	DMj	Inactive	Atopic dermatitis	4
4	M	82	ADM	Active	Chronic bronchitis	5
5	F	49	DMad	Active		2
6	F	56	DMad	Inactive		1
7	F	33	ADM	Active	Seborrheic dermatitis	5
8	F	75	DMad	Active		7
9	F	28	DMad	Active	Seborrheic dermatitis	5
10	F	79	DMad	Inactive		1
11	M	53	DMad	Active		1
12	F	70	DMad	Active		3
13	M	36	DMad	Active	Atopic dermatitis	2
14	M	42	DMm	Active	Squamous cell carcinoma of the pyriform sinus	2
15	F	53	DMad	Active		2
16	M	65	DMad	Active		1

Abbreviations: ADM, amyopathic dermatomyositis; DMad: adult dermatomyositis; DMc, dermatomyositis associated with connective tissue disease; DMj: juvenile dermatomyositis; DMm, dermatomyositis associated with malignancy; M, male; F, female.

were observed between the control group and inactive dermatomyositis (*P*=.4197).

In the analysis of SC5b-9, the difference between means in the control group and patients with active dermatomyositis was 1.3160 (−1.9846 to −0.6475) (*P*=.0002). There were no statistically significant differences between active and inactive dermatomyositis or between inactive dermatomyositis and the control group. Given that only 8 observations were available for patients with inactive dermatomyositis, it was unfeasible to estimate, with any degree of precision, the sensitivity and specificity of C3a-desArg or SC5b-9 as markers of disease activity.

Correlation Between Skin, Muscle, and Total Activity and Levels of the Different Biochemical Markers Analyzed

With some exceptions, positive correlation coefficients were obtained for C3a-desArg and SC5b-9 compared with skin and muscle scores, although the values were very dispersed (Table 4). Aldolase, CPK, and LDH were positively correlated with both clinical activity parameters. Aspartate aminotransferase and ALAT were generally positively correlated with skin scores but the correlation varied when considering muscle scores. Both positive and negative correlations were observed with ESR, C3, and C4. In patient 9, muscle scores showed a negative correlation with most biochemical markers of myositis.

Due to the low number of observations, not all the correlations reached statistical significance. Therefore, the patients were measured as a single group. These estimations of the Spearman rank correlation coefficient are shown in Table 5. The CAP C3a-desArg only displayed a positive correlation with the skin scores. There was no statistically significant relationship between SC5b-9 and any of the clinical activity parameters. Skin scores were significantly correlated with ASAT, ALAT, LDH, and aldolase concentrations. Muscle and overall scores did not show a significant correlation with any of these variables.

Association Between Levels of Biochemical Markers and Recrudescence

Six episodes of recrudescence were identified during follow-up. Values of C3a-desArg and SC5b-9 above the 95th percentile of the normal range determined in the control group calculated by nonparametric methods (177.04 ng/mL and 61.12 ng/mL, respectively) were considered abnormally high.

Table 3. Concentrations of C3a-desArg and SC5b-9

		Median	*Mean*	*SD*
Control group	C3a-desArg	50.42	52.43	16.46
	SC5b-9	3.89	6.63	8.01
Inactive DM	C3a-desArg	47.29	57.50	25.36
	SC5b-9	9.15	12.70	13.15
Active DM	C3a-desArg	75.45	107.81	123.40
	SC5b-9	20.05	43.76	116.38

Abbreviation: DM, dermatomyositis.
Difference between C3a-desArg levels in active dermatomyositis and control group, *P*<.0001.
Difference between C3a-desArg levels in active and inactive dermatomyositis, *P*=.0066.
Difference between SC5b-9 levels in active and inactive dermatomyositis, *P*=.0002.

Relationship Between Clinical Recrudescence and Increases in Plasma Levels of C3a-desArg and SC5b-9 in the Previous 4 Months

Increases in the levels of C3a-desArg and SC5b-9 observed between successive visits were assessed to evaluate their association with later clinical recrudescences of the process. These increases were expressed as percentages of the previously obtained value for the variable (Table 6).

When assessing the specificity and sensitivity of the different biochemical variables as predictors of recrudescence, only those measurements were considered for which subsequent clinical assessments were available to confirm or rule out the existence of clinical recrudescence (4 clinical recrudescences and 18 assessment intervals). Increases in C3a-desArg levels were identified in the 4 recrudescences assessed and in 3 of the 18 assessment intervals unrelated to later recrudescences. Previous increases in SC5b-9 were observed in 3 of the 4 recrudescences and in 4 of the 18 intervals unrelated to later recrudescences. Thus, C3a-desArg and SC5b-9 had a sensitivity of 100% and 75%, respectively, and a specificity of 83.3% and 77.7%, respectively, to predict recrudescences in the 4 following months. Efficacy was 86.3% for C3a-desArg and 77.2% for SC5b-9, and the positive predictive value or absolute risk of clinical recrudescence in the 4 months after an increase in plasma levels was 57.1% for C3a-desArg and 42.8% for SC5b-9.

Table 4. Spearman Rank Correlation Coefficients by Patient

Patient	*Activity*	*C3a*	*C5b-9*	*ASAT*	*ALAT*	*CPK*	*Aldolase*	*LDH*	*ESR*	*C3*	*C4*
1	Skin	0.94[a]	0.84[a]	0.31	-0.71	0.86[a]	0.8	0.6	0.97[a]	-0.48	-0.08
	P	.0048[a]	.0361[a]	.5379	.1108	.0244[a]	.2	.208	.0012[a]	.3287	.8717
	Muscle	0.94[a]	0.89[a]	0.24	-0.45	0.83[a]	0.63	0.51	0.9[a]	-0.45	0.03
	P	.0051[a]	.0165[a]	.6379	.3641	.0401[a]	.3675	.2946	.0127[a]	.3641	.9545
	Total	0.94[a]	0.84[a]	0.32	-0.71	0.86[a]	0.8	0.6	0.97[a]	-0.48	-0.08
	P	.0048[a]	.0361[a]	.5379	.1108	.0244[a]	.2	.208	.0012[a]	.3287	.8717
2	Skin	0.2	0.37	0.14	0.17	0.42	0	-0.31	-0.94[a]	-0.8	-0.8
	P	.704	.4685	.7872	.7417	.3965	1	.5441	.0048[a]	.1041	.1041
	Muscle	0.27	0.33	-0.06	0.18	0.16	0.33	0.1	-0.77	-0.35	-0.7
	P	.6042	.5122	.8987	.7204	.7489	.5811	.8484	.0687	.5594	.1817
	Total	0.2	0.37	0.14	0.17	0.42	0	-0.31	-0.94[a]	-0.8	-0.8
	P	.704	.4685	.7872	.7417	.3965	1	.5441	.0048[a]	.1041	.1041
3[b]	Skin	–	–	–	–	–	–	–	–	–	–
	P										
	Muscle	–	–	–	–	–	–	–	–	–	–
	P										
	Total	–	–	–	–	–	–	–	–	–	–
	P										
4	Skin	0.4	-0.15	0.41	0.3	-0.4	0.8	0	0.3	-0.4	-0.4
	P	.5046	.8046	.4925	.6144	.5046	.2	1	.6238	.6	.6
	Muscle	–	–	–	–	–	–	–	–	–	–
	P										
	Total	0.4	-0.15	0.41	0.3	-0.4	0.8	0	0.3	-0.4	-0.4
	P	.5046	.8046	.4925	.6144	.5046	.2	1	.6238	.6	.6
7	Skin	0	0.9[a]	0.8	0.82	0.15	0	0.3	-0.31	-0.1	-0.1
	P	1	.0374[a]	.1041	.0886	.8046	1	.6238	.6838	.8729	.8729
	Muscle	–	–	–	–	–	–	–	–	–	–
	P										
	Total	0	0.9[a]	0.8	0.82	0.15	0	0.3	-0.31	-0.1	-0.1
	P	1	.0374[a]	.1041	.0886	.8046	1	.6238	.6838	.8729	.8729
8	Skin	0.69	0.63	0.72	0.51	-0.04	0.09	0.48	0.3	-0.28	0.24
	P	.0847	.1245	.626	.232	.92	.8419	.2682	.5518	.542	.5991
	Muscle	0.63	0.9[a]	0.54	0.84[a]	-0.22	0.32	0.43	0.35	-0.1	0.41
	P	.1243	.0045[a]	.2053	.0159[a]	.6352	.4736	.3276	.4924	.8159	.3504
	Total	0.66	0.86[a]	0.57	0.77[a]	-0.21	0.25	0.45	0.31	-0.12	0.37
	P	.1019	.012[a]	.1754	.0411[a]	.6384	.5852	.3104	.5379	.7876	.4026
9	Skin	0.6	0.7	0.9[a]	1	0.3	0.9[a]	0.8	0.35	0	0.2
	P	.2848	.1881	.0374[a]	<.0001[a]	.6238	.0374[a]	.1041	.5528	1	.7471
	Muscle	-0.87	-0.87	-0.56	-0.56	-0.05	-0.66	-0.66	-0.78	-0.56	0.56
	P	.0539	.0539	.3217	.3217	.9347	.2189	.2189	.1122	.3217	.3217
	Total	-0.9[a]	-0.8	-0.6	-0.5	-0.2	-0.6	-0.7	-0.66	-0.5	0.7
	P	.0374[a]	.1041	.2848	.391	.7	.2848	.1881	.2189	.391	.1881

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CPK, creatine phosphokinase; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

[a]Statistically significant (*P*<.05).

[b]Correlations could not be evaluated due to skin and muscle scores remaining invariable throughout follow-up.

Table 5. Spearman Rank Correlation Coefficients for the Overall Group

Activity	*C3a*	*C5b-9*	*ASAT*	*ALAT*	*CPK*	*Aldolase*	*LDH*	*ESR*	*C3*	*C4*
Skin	0.43[a]	0.31	0.53[a]	0.45[a]	0.39	0.5a	0.43[a]	0.02	-0.23	-0.1
P	.0351[a]	.1291	.0072[a]	.0264[a]	.0542	.0208[a]	.0343[a]a	.9063	.2805	.6388
No.	24[a]	24	24[a]	24[a]	24	21	24[a]	23	23	23
Muscle	0.2	0.16	0.1	-0.11	0.14	-0.23	-0.18	-0.13	-0.18	0.18
P	.3448	.4313	.6218	.6071	.4849	.3121	.3947	.5306	.4083	.4018
No.	24	24	24	24	24	21	24	23	23	23
Total	0.13	0.08	0.25	-0.02	0.3	-0.04	-0.09	-0.21	-0.37	0.15
P	.5419	.6949	.2214	.9211	.1414	.836	.6638	.3284	.0806	.4765
No.	24	24	24	24	24	21	24	23	23	23

Abbreviations: ASAT: aspartate aminotransferase; ALAT, alanine aminotransferase; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate.
[a]Statistically significant (*P*<.05).

Relationship between Increases in Traditional Biochemical Markers of Activity and Recrudescence

The respective values for sensitivity and specificity of 20% variations in previous levels to predict recrudescence in the 4 following months were as follows: ASAT (25%, 88.8%), ALAT (25%, 94.4%), LDH (75%, 94.4%), CPK (75%, 88.8%), aldolase (33.3%, 81.2%), VSG (50%, 75%), C3 (0%, 100%), and C4 (0%,100%). The diagnostic yield as markers of recrudescence for each variable was as follows: ASAT (77.27%), ALAT (81.8%), LDH (90.9%), CPK (86.3%), aldolase (73.6%), ESR (70%), C3 (80%), and C4 (80%).

The positive predictive value or absolute risk of developing a clinical recrudescence in the 4 months after a positive test result was as follows: ASAT (33.3%), ALAT (50%), LDH (75%), CPK (60%), aldolase (25%), and ESR (33.3%). This could not be assessed for C3 and C4.

Discussion

Comparison of Plasma Levels of C3a-desArg and SC5b-9 with Disease Activity

The observation of increases in C3a-desArg and SC5b-9 levels in patients with dermatomyositis suggests that complement system activation is involved in the pathogenesis of the disease. The results also demonstrate that C3a-desArg levels tend to be higher in the patients with active disease. On the other hand, significant differences in SC5b-9 levels were only observed between patients with active disease and the control group, while no significant differences were observed between these patients and patients with clinically inactive disease. Thus, periodic analysis of C3a-desArg plasma levels would be useful to differentiate between patients with active and

Table 6. Increases in C3a-desArg and SC5b-9 Levels in Prospective Analyses

CAP	*Patient*	*Visit*	*% increase*	*Recrudescence in the Following 4 Months*
C3a-desArg	1	4	20.88	No
C3a-desArg	2	3	16.26	Yes
C3a-desArg	3	2	6.05	No
C3a-desArg	3	3	41.43	No
C3a-desArg	4	2	52.77	No
C3a-desArg	7	4	12.72	Yes
C3a-desArg	8	6	579.07	Yes
C3a-desArg	9	3	324.05	Yes
SC5b-9	1	2	104.67	No
SC5b-9	1	5	15.41	No
SC5b-9	2	3	19.26	Yes
SC5b-9	2	5	1,797.13	No
SC5b-9	3	2	150	No
SC5b-9	3	3	319.48	No
SC5b-9	4	2	4.46	No
SC5b-9	7	4	46.98	Yes
SC5b-9	8	6	9.8	Yes
SC5b-9	9	3	625.22	Yes

Abbreviation: CAP, complement activation product.

inactive dermatomyositis. In a previous study by Scott and Arroyave,[28] high levels of C3d were observed in 6 out of 7 patients with dermatomyositis and were also higher in those with active disease, findings which are consistent with the results for C3a-desArg obtained here. The low number of measurements in patients with inactive disease and the dependency of the observations on each patient make it impossible to determine the sensitivity and specificity of these 2 analytical parameters as markers of dermatomyositis activity.

In the 2 patients with amyopathic dermatomyositis, the variations in plasma levels of CAP were exclusively attributable to skin activity during the disease process, and positive correlations were observed between them. This observation is consistent with the involvement of complement system activation in the pathogenesis of the skin lesions characteristic of the disease.

The observation of negative correlations between muscle parameters and most markers in patient number 9 should be noted. It was shown that the worsening of the muscle condition in that patient was due to the development of muscle atrophy or steroid myopathy, in the context of progressive improvement in the remaining parameters of disease activity. This would account for increased signs of muscle impairment, despite decreased levels of biochemical markers of activity, and explain the negative sign of the correlation coefficient.

A positive correlation was observed between C3a-desArg and SC5b-9 levels and signs of skin and muscle activity, although the values varied depending on the patient, with a trend toward higher values (higher than 0.5) between SC5b-9 and skin activity. Unexpectedly, these markers of complement activation did not present higher correlations with the parameters of clinical activity than the other traditional markers of activity.

The positive correlation between the parameters of skin activity and biochemical markers of myositis (CPK, aldolase, ASAT, ALAT and LDH) in most patients was striking. This can be attributed to the parallel course of dermatomyositis-related skin and muscle disorders in most patients. Furthermore, it was demonstrated that the biochemical parameters of myositis displayed a better correlation with the parameters of skin activity than with muscle strength, as assessed in the physical examination. Although the evaluation of muscle strength has a reasonable degree of objectivity, it is probably limited as it cannot detect smaller changes in the extent to which strength is affected. On the other hand, skin damage, which can be assessed "more objectively," can more accurately reflect the inflammatory activity of the disease process as a whole. These results would justify including a detailed description of skin damage in the measurement scales of disease activity, as proposed by other authors.[72]

Of equal significance is the high correlation between ESR and the parameters of clinical activity in patients 1 and 2. In patient 1, the correlation was positive, although the patient presented other associated autoimmune processes (Hashimoto thyroiditis and Sjögren syndrome). Patient 2 had dermatomyositis associated with malignancy and the correlation was negative. This was attributed to increased ESR levels caused by metastasis in a patient in whom clinical symptoms of dermatomyositis improved after treatment with high doses of systemic corticosteroids.

Due to consumption of C3 and C4 secondary to the inflammatory activity of the process, predominantly negative within-patient correlation was observed between these complement factors and disease activity. As other authors have observed in other autoimmune processes, such as systemic lupus erythematosus (SLE),[73,74] the correlation coefficients were somewhat higher for C3, and this was attributed to activation of the complement system mainly via the classical pathway. The correlation coefficients for C3a-desArg and SC5b-9 were generally higher than those for C3 and C4 in the same patient, a finding which was consistent with the results described by other authors for SLE.[69-75]

Correlation Between Skin, Muscle, and Total Activity and Activity Markers when Assessing the Patient Group Together

The results suggest that C3a-desArg exhibits a stronger correlation with the parameters of dermatomyositis activity than does SC5b-9. While studies have been published on other diseases, such as SLE,[69] showing similar results to those reported here, others have suggested that SC5b-9 is the CAP that better correlates with disease activity.[74-76]

Nevertheless, it should be taken into account that the relatively weak correlation between C3a-desArg and the skin scores and the absence of correlation of this CAP with the muscle scores, and of SC5b-9 with all the clinical activity parameters, could be due to the low number of patients for whom sufficient data were available to perform the analysis.

Analysis of traditional markers of activity revealed a significant correlation between the levels of LDH, ASAT, ALAT, LDH, and aldolase and the skin scores. There was no significant correlation between this clinical parameter and the other traditional biochemical markers (ESR, C3, and C4). Furthermore, there were no significant correlations between muscle scores and any of these variables. Creatine phosphokinase, which is considered the most useful muscle enzyme for use in follow-up of patients with dermatomyositis, exhibited a somewhat

weaker correlation than the other enzymes that was not statistically significant. Thus, taking the patient group as a whole, and in contrast to the study hypothesis, it was shown that the correlation between disease activity and CAP levels is lower than that obtained with traditional markers. Therefore, C3a-desArg and SC5b-9 are no more useful than other biochemical markers in assessing dermatomyositis activity at a given time-point during follow-up.

One possible interpretation of this weak correlation is that the increase in CAP levels precedes clinical recrudescence and therefore precedes the variation in clinical activity parameters (Figure). Muscle enzymes are released as a consequence of muscle fiber damage, and there is therefore a stronger correlation between increasing concentrations of those markers and the development of muscle weakness over time. The establishment of immunomodulatory therapy would also explain the inhibition of the pathogenic mechanism and, thus, the decrease in CAP levels preceding functional recovery of the target tissues. This time-lag between variations in CAP levels and clinical scores could explain the weak correlation obtained for these markers.

Periodic and Serial Measurement of C3a-desArg and SC5b-9 as Predictors of Recrudescence of the Disease. Comparison with Traditional Markers of Activity

Given the lack of previous studies on dermatomyositis, we used studies of SLE as a reference to establish 4 months as the period prior to recrudescence to assess the levels of different biochemical markers.[70,75] Out of the 4 recrudescences considered, we found previous abnormally high levels of C3a-desArg in just 2 patients and SC5b-9 in 1; these were associated with serious symptoms or visceral involvement. In relation to these patients, on 2 and 1 occasions, respectively, we observed abnormally high levels that were not related to later recrudescence. Thus, isolated measurements of CAP levels do not seem to offer sufficient sensitivity and specificity to predict recrudescence in patients with dermatomyositis. The high between-individual variability of CAP plasma levels, even between control patients, could be responsible for this.

Thus, it seems appropriate to assess changes in the level of complement activation through identifying prospective variations in CAP levels in each patient. We observed that in all the patients in whom recrudescence was observed, increased levels of C3a-desArg were detected in the 4 previous months. These increases were greater than 12% in all the patients and reached 300% and 500% in 2 patients. Levels of SC5b-9 increased in 3 of the 4 recrudescences assessed and decreased in 1 during the previous months. The observed increases were more than 19% and reached 600% on 1 occasion. The greatest increases in levels of the 2 CAP were associated with serious recrudescences involving extensive necrotic skin lesions or with the development of interstitial lung disease.

The increases in C3a-desArg and SC5b-9 that were unrelated to later recrudescence coincided with the development of acute bronchitis symptoms (patient 4) and ulcerative pancolitis (patient 3). Only on 1 occasion was no concurrent process identified that could explain the increase. The data suggest that prospective increases in plasma levels of CAP, especially in C3a-desArg, have high sensitivity for predicting recrudescence of the disease and that there is an association between the degree of this increase and the severity of the recrudescence. We observed that, under the study conditions, variations in C3a-desArg

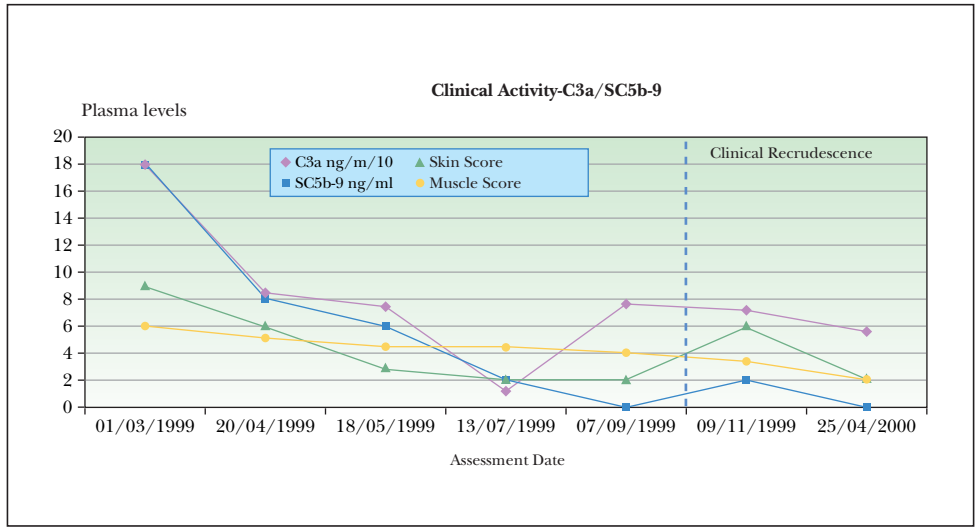

Figure. Levels of C3a-desArg/SC5b-9 and recrudescence in patient 8.

levels were the most sensitive indicator for predicting recrudescence, with a sensitivity of 100%. This was followed by variations in SC5b-9, LDH, and CPK levels, with a sensitivity of 75%, and then variations in ESR levels, with a sensitivity of 50%. The special sensitivity of CAP was clear in patient 9, who developed serious recrudescence with deterioration of muscle strength and the appearance of interstitial lung disease—the only assessable increases observed in that patient were seen in the levels of C3a-desArg and SC5b-9. Finally, under the given study conditions, the increase in C3a-desArg levels compared to previous values would be the most sensitive marker for predicting clinical recrudescence in patients with dermatomyositis, and the specificity using that marker is high.

In conclusion, our results indicate that the complement system is activated in the patients with dermatomyositis and that the degree of that activation is related to the level of disease activity. Nevertheless, isolated measurements of CAP levels are of limited use in establishing disease activity. Only the identification of very high levels of C3a-desArg can contribute to the prediction of serious recrudescence in later months. The serial measurement of C3a-desArg would be the most sensitive parameter for predicting recrudescence of the disease, there being a correlation between the severity of recrudescence and C3a-desArg levels. Multicenter studies involving a sufficient number of cases and recrudescences will be required to confirm our findings. On the other hand, plasma levels of C3a-desArg and SC5b-9 could be useful in distinguishing muscle weakness secondary to myositis from steroid myopathy or secondary muscle atrophy in patients being treated for dermatomyositis.

In conclusion, the determination of plasma levels of CAP appears to be an additional tool that can be used in the clinical follow-up of patients with dermatomyositis—especially in those with unstable or serious forms—by contributing to the prediction of recrudescence.

Conflicts of Interest

The authors declare no conflicts of interest.

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