

Characterization of a subset of patients with primary Sjögren's syndrome initially presenting with C3 or C4 hypocomplementemia

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Abstract

Objective: This study aimed to determine the association of C3 and C4 hypocomplementemia at the diagnosis of primary Sjögren's syndrome (pSS) with clinical manifestations, disease activity, and disease damage.

Methods: A cross-sectional study was conducted in 94 Puerto Ricans with pSS. Patients were aged ≥ 21 years and met the 2012 American College of Rheumatology Classification Criteria for pSS. Demographic characteristics, health-related features, cumulative extraglandular manifestations, serologic tests at pSS diagnosis, comorbidities, disease activity (per European League Against Rheumatism Sjögren's Syndrome Disease Activity Index [ESSDAI]), disease damage (per Sjögren's Syndrome Disease Damage Index [SSDDI]), and pharmacologic therapy were determined. Serum C3 and C4 levels were measured at pSS diagnosis by immunoturbidimetry. Patients with and without hypocomplementemia were analyzed using bivariate and multivariate logistic regression analyses adjusted for age, sex, and disease duration.

Results: The mean age and disease duration of the study population were 52.4 ± 12.4 years and 5.9 ± 4.8 years, respectively; of the total study population, 94% were female. C3 and C4 hypocomplementemia were observed in 9.6% and 13.8% of the patients, respectively. In the multivariate analysis, C3 hypocomplementemia was associated with leukocytoclastic vasculitis, interstitial lung disease, higher SSDDI score, and exposure to rituximab. C4 hypocomplementemia was associated with leukocytoclastic vasculitis, interstitial lung disease, and higher ESSDAI and SSDDI scores.

Conclusion: In this population of patients with pSS, low C3 and C4 levels at diagnosis were associated with extraglandular manifestations such as vasculitis and interstitial lung disease, as well as disease activity and damage accrual. These results suggest that complements C3 and C4 have clinical and prognostic value in patients with pSS.

Keywords: Sjögren's syndrome, C3 complement, C4 complement

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Introduction

Primary Sjögren's syndrome (pSS) is a progressive autoimmune disease characterized by lymphocytic infiltration primarily of the exocrine glands (1). Clinical presentation ranges from sicca symptoms to extraglandular manifestations such as musculoskeletal, pulmonary, renal, and nervous system involvement, among others (2). In contrast to other rheumatic autoimmune diseases such as systemic lupus erythematosus, the association of serologic markers with clinical features of pSS has not been well established, except for C3 and C4 hypocomplementemia, which has been identified as a risk factor for lymphoma (3). Few studies have shown that low serum C3 and C4 levels correlate with specific extraglandular manifestations such as vasculitis, disease activity, and damage accrual (4-6). It is likely that these serologic markers are not frequently used in this clinical setting because low C3 and C4 levels are found at diagnosis in only 1%-15% of patients with pSS and in about 20% during the course of the disease (7, 8). Nonetheless, those who present with C3 and C4 hypocomplementemia could represent a subset of patients with a poorer disease course and outcome. Hence, we sought to evaluate the association of low C3 and C4 levels at pSS diagnosis with clinical manifestations, disease activity, and disease damage.

Methods

Patient population

We performed a cross-sectional study in 94 Puerto Ricans with pSS evaluated from August 2014 to August 2017. Patients were adults (aged ≥ 21 years), and all met the 2012 American College of Rheumatology

Classification Criteria for pSS (9). As stated in this classification, patients with the following conditions were excluded: secondary Sjögren's syndrome, IgG4 disease, sarcoidosis, lymphoma, history of head and neck radiation, graft-versus-host disease, and infection with hepatitis C virus and human immunodeficiency virus. This study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (Approval Date: May 19, 2014; Approval Number: A6310114). Signed consent was waived because this research presented no more than minimal risk of harm to subjects, and involved no procedures for which written consent is normally required as the information gathered for this the study was obtained during routine medical visits and it was within standards of care for pSS patients.

Variables

Factors from the following domains were determined: demographic features, lifestyle behaviors, extraglandular manifestations, serologic markers, disease activity, disease damage, comorbidities, and pharmacologic profile. Age, gender, and disease duration (period between pSS diagnosis and study visit) were included in the demographic domain. Lifestyle behaviors such as alcohol intake (≥ 1 drink per day for women and ≥ 2 drinks per day for men), exercise (structured or planned physical activity at least 3 times per week), and tobacco use were noted at the study visit. At any time during the course of pSS, the presence of the following extraglandular manifestations was determined: arthralgia, arthritis, urticarial rash, peripheral neuropathy (pure sensory or mixed polyneuropathy, diagnosed by electrophysiological studies), leukocytoclastic vasculitis (diagnosed by skin biopsy), interstitial lung disease (diagnosed by high-resolution chest computed tomography), autoimmune hepatitis (diagnosed by liver biopsy), renal tubular acidosis, anemia, leukopenia ($< 4,000/\text{mm}^3$), neutropenia ($< 1,500/\text{mm}^3$), lymphopenia ($< 1,000/\text{mm}^3$), thrombocytopenia ($< 100,000/\text{mm}^3$),

and hypergammaglobulinemia. The following serologic markers were measured at the diagnosis: antinuclear antibodies, rheumatoid factor, anti-Ro and anti-La antibodies, and C3 and C4 complements. Serum C3 and C4 levels were measured by immunoturbidimetry. These levels were defined as low according to the standard laboratory parameters. Normal range for serum C3 and C4 was 80-160 mg/dL and 16-48 mg/dL, respectively.

Disease activity was determined at the study visit using the 2010 European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) (10) and disease damage was determined using the Sjögren's Syndrome Disease Damage Index (SSDDI) (11). Cumulative selected comorbidities and pSS pharmacologic treatments (muscarinic agonists, nonsteroidal anti-inflammatory drugs, corticosteroids, hydrochloroquine, and immunosuppressive drugs) were ascertained at the study visit.

Statistical analysis

Patients with and without low C3 and C4 levels were compared using Fisher's exact test, Chi-square test, Student's t test, and Mann-Whitney test, as appropriate. Factors that were significant in the bivariate analysis were entered into the multivariate logistic regression analyses adjusted for age, sex, and disease duration. Statistical significance was established at $p < 0.05$. Statistical analysis was performed using the STATA v.15 (StataCorp; College Station, TX, USA).

Results

A total of 94 patients were studied, of whom 88 (93.6%) were females. The mean (standard deviation [SD]) age of the study population was 52.4 (12.4) years. The mean (SD) disease duration was 5.9 (4.8) years. At pSS diagnosis, low C3 and C4 levels were found in 9 (9.6%) and 13 (13.8%) patients, respectively. Moreover, 7 (7.4%) patients had both C3 and C4 hypocomplementemia.

Table 1 shows the demographic features, lifestyle behaviors, clinical manifestations, serologic tests, disease activity, and damage accrual in patients with and without hypocomplementemia. No significant differences were observed for age, gender, disease duration, and health-related behaviors between the study groups. Patients with low C3 levels were more likely to have leukocytoclastic vasculitis (44.4% vs. 8.2%, $p = 0.010$), interstitial lung disease (33.3% vs. 1.2%, $p = 0.002$), and higher SSDDI scores (2.2 ± 2.2 vs. 0.5 ± 0.9 , $p = 0.002$) than those with normal C3 levels. In contrast, leukocytoclastic vasculitis (38.5% vs.

7.4%, $p = 0.007$), interstitial lung disease (23.1% vs. 1.2%, $p = 0.008$), and higher ESSDAI (1.5 ± 1.7 vs. 0.6 ± 0.8 , $p = 0.013$) and SSDDI (2.00 ± 2.20 vs. 0.48 ± 0.76 , $p = 0.003$) scores were more commonly seen in patients with low C4 levels compared with those with normal levels.

Selected comorbid conditions are shown in Table 2. Patients with low C3 levels had asthma (33.3% vs. 7.1%, $p = 0.039$) more frequently than those with normal C3 levels. No significant differences were found for other comorbidities. Patients with low C3 levels were more frequently exposed to rituximab treatment (22.2% vs. 2.4%, $p = 0.045$) than those with normal C3 levels. No significant differences were found for other pharmacologic therapies (Table 3).

Table 4 depicts the multivariate logistic regression of features associated with low C3 and C4 levels. Low C3 levels were related to leukocytoclastic vasculitis (odds ratio [OR]: 9.53, 95% confidence interval [CI]: 1.73-52.48), interstitial lung disease (OR: 43.43, 95% CI: 3.51-536.80), SSDDI score ≥ 1 (OR: 3.11, 95% CI: 1.49-6.47), and rituximab therapy (OR: 112.63, 95% CI: 5.51-2,304.04). Low C4 levels were associated with leukocytoclastic vasculitis (OR: 5.41, 95% CI: 1.02-28.70), interstitial lung disease (OR: 40.87, 95% CI: 3.21-519.77), ESSDAI score ≥ 1 (OR: 1.86, 95% CI: 1.05-3.29), and SSDDI score ≥ 1 (OR: 2.71, 95% CI: 1.37-5.35).

Discussion

This study evaluated the relationship of C3 and C4 hypocomplementemia with extraglandular manifestations, disease activity, and disease damage in patients with pSS initially presenting with C3 or C4 hypocomplementemia. We found that low C3 and C4 levels seem to have a significant clinical and prognostic value in patients with pSS. Our data show that C3 and C4 hypocomplementemia are associated with major clinical manifestations such as leukocytoclastic vasculitis and interstitial lung disease and with damage accrual. C4 hypocomplementemia, but not C3, was also associated with disease activity.

Our study confirms the association of C3 and C4 hypocomplementemia with vasculitis (12). For example, in a Spanish cohort of patients with pSS, leukocytoclastic vasculitis was found to be the main histologic diagnosis in 95% of patients with vasculitis, and 49% of them had C3 and C4 hypocomplementemia (13). This association is not surprising because leukocytoclastic vasculitis is an immune complex disease; thus, complement fixation and consumption are expected.

Main Points

- The association of C3 or C4 hypocomplementemia (at diagnosis) with extraglandular manifestations, disease activity, and damage accrual in patients with primary Sjögren's syndrome was evaluated.
- Low serum levels of C3 and C4 were associated with leukocytoclastic vasculitis, interstitial lung disease, and disease damage.
- C4 hypocomplementemia correlated with disease activity.

Table 1. Demographic features, lifestyle behaviors, clinical manifestations, serologic tests, disease activity, and damage accrual in patients with pSS.

Features	C3 complement levels			C4 complement levels		
	Normal (n=85)	Low (n=9)	p	Normal (n=81)	Low (n=13)	p
Age, mean (SD) years	52.7 (12.6)	49.3 (10.3)	0.443	53.3 (12.4)	45.7 (12.4)	0.047
Gender, % female	94.1	88.9	0.463	93.8	92.3	0.999
Disease duration, mean years (SD)	5.6 (4.2)	8.7 (8.4)	0.568	5.5 (4.2)	8.7 (7.2)	0.160
Lifestyle behaviors, %						
Alcohol consumption	5.9	11.1	0.463	4.9	15.4	0.192
Cigarette smoking	4.7	0.0	0.999	3.7	7.7	0.454
Exercise	28.2	33.3	0.713	27.2	38.5	0.510
Extraglandular manifestations, %						
Arthralgia	82.4	88.9	0.999	82.7	84.6	0.999
Arthritis	24.7	44.4	0.240	24.7	38.5	0.321
Urticarial rash	4.7	22.2	0.100	4.9	15.4	0.192
Pure sensory neuropathy	17.7	44.4	0.078	21.0	15.4	0.999
Mixed polyneuropathy	10.6	0.0	0.593	11.1	0.0	0.352
Leukocytoclastic vasculitis	8.2	44.4	0.010	7.4	38.5	0.007
Interstitial lung disease	1.2	33.3	0.002	1.2	23.1	0.008
Autoimmune hepatitis	2.4	0.0	0.999	2.5	0.0	0.999
Renal tubular acidosis	1.2	0.0	0.999	1.2	0.0	0.999
Anemia	37.7	22.2	0.480	34.6	46.2	0.536
Leukopenia (<4,000/mm ³)	32.1	22.2	0.715	32.1	25.0	0.748
Neutropenia (<1,500/mm ³)	7.1	11.1	0.522	6.2	16.7	0.222
Lymphopenia (<1,000/mm ³)	26.2	33.3	0.698	25.0	38.5	0.325
Thrombocytopenia (<100,000/mm ³)	7.1	0.0	0.999	6.2	8.3	0.574
Hypergammaglobulinemia	28.2	11.1	0.436	24.7	38.5	0.321
Serologic tests, %						
Antinuclear antibodies	84.3	77.8	0.637	83.7	83.3	0.999
Rheumatoid factor	57.3	50.0	0.723	56.4	58.3	0.900
Anti-Ro antibodies	85.9	77.8	0.618	86.4	76.9	0.403
Anti-La antibodies	37.7	44.4	0.728	37.0	46.2	0.530
Anti-Ro and anti-La antibodies	36.5	44.4	0.723	35.8	46.2	0.543
ESSDAI						
Activity index score, mean (SD)	0.6 (0.9)	1.1 (1.5)	0.248	0.6 (0.8)	1.5 (1.7)	0.013
Activity index score ≥1, %	42.4	66.7	0.290	39.5	76.9	0.012
SSDDI						
Damage index score, mean (SD)	0.5 (0.9)	2.2 (2.2)	0.002	0.5 (0.8)	2.0 (2.2)	0.003
Damage index score ≥1, %	36.5	77.8	0.028	35.8	69.2	0.023

ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; pSS: primary Sjögren's syndrome; SD: standard deviation; SSDDI: Sjögren's Syndrome Disease Damage Index.

Table 2. Comorbid conditions in patients with pSS.

Comorbidities, %	C3 complement levels			C4 complement levels		
	Normal (n=85)	Low (n=9)	p	Normal (n=81)	Low (n=13)	p
Hypertension	37.7	44.4	0.728	40.7	23.1	0.224
Type 2 diabetes mellitus	12.9	0.0	0.592	13.6	0.0	0.352
Dyslipidemia	36.5	11.1	0.160	38.3	7.7	0.054
Overweight/obesity (BMI \geq 25.0)	66.2	55.6	0.713	65.7	61.5	0.761
Coronary artery disease	4.7	0.0	0.999	4.9	0.0	0.999
Hypothyroidism	32.9	44.4	0.484	34.6	30.8	0.999
Asthma	7.1	33.3	0.039	7.4	23.1	0.107
Osteoarthritis	42.4	44.4	0.999	45.7	23.1	0.126
Osteoporosis	12.9	33.3	0.129	16.1	7.7	0.683
Fibromyalgia	18.8	0.0	0.349	19.8	0.0	0.115
Depression	25.9	33.3	0.696	25.9	30.8	0.740
Headaches	5.9	11.1	0.463	6.2	7.7	0.999
Peptic ulcer disease/gastritis	22.4	0.0	0.196	21.0	15.4	0.999
Infections (any cause)	27.1	33.3	0.704	25.9	38.5	0.339
Neoplasia	7.1	0.0	0.999	4.9	16.7	0.171

BMI: body mass index; pSS: primary Sjögren's syndrome.

Table 3. Pharmacologic treatment in patients with pSS.

Medications, %	C3 complement levels			C4 complement levels		
	Normal (n=85)	Low (n=9)	p	Normal (n=81)	Low (n=13)	p
Pilocarpine	8.4	11.1	0.576	7.5	16.7	0.279
Cevimeline	44.7	33.3	0.727	44.4	38.5	0.686
Cyclosporine (ophthalmic)	27.1	33.3	0.704	29.6	15.4	0.504
NSAIDs	48.2	55.6	0.737	50.6	38.5	0.416
Prednisone	31.8	55.6	0.265	30.9	53.9	0.123
Hydroxychloroquine	89.4	77.8	0.283	87.7	92.3	0.999
Methotrexate	7.1	12.5	0.479	6.2	16.7	0.222
Azathioprine	4.7	11.1	0.402	4.9	7.7	0.533
Rituximab	2.4	22.2	0.045	2.5	15.4	0.091

NSAIDs: Nonsteroidal anti-inflammatory drugs; pSS: Primary Sjögren's syndrome.

We found that patients with C3 and C4 hypocomplementemia at diagnosis were more likely to have interstitial lung disease than those with normal complement levels. However, previous studies are conflictive regarding this association. In a multicenter cohort study of Chinese patients with pSS, hypocomplementemia was not found to be a risk factor for interstitial lung disease (14). Another study in Asian patients with pSS, did not find any differences in C3 and C4 levels in patients with and without

interstitial lung disease (15). On the contrary, studies performed in populations from Spain, Argentina, and Italy have reported associations of C3 or C4 hypocomplementemia with interstitial lung disease in pSS (16-18). The discrepancies observed between these studies, including ours, could be related to geographic and ethnic factors.

In the bivariate analysis, we found an association between C3 hypocomplementemia and

asthma. Interestingly, patients with pSS appear to have a higher risk of developing asthma compared with those without pSS (19). In fact, other investigators have reported the association of low C3 levels in the general population of patients who have asthma (20). It has been shown that C3a plays a critical role by regulating the interaction between mast cells and bronchial smooth muscle cells in lung inflammation in patients who have asthma (21). Therefore, the activation of complement cas-

Table 4. Logistic regression of characteristics associated with C3 and C4 hypocomplementemia in patients with pSS.

Characteristics	Low C3 complement levels		Low C4 complement levels	
	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)	Characteristics	Unadjusted OR (95% CI)
Leukocytoclastic vasculitis	8.91 (1.94-40.98)	9.53 (1.73-52.48)	7.81 (1.94-31.45)	5.41 (1.02-28.70)
Interstitial lung disease	11.86 (1.44-97.44)	43.43 (3.51-536.80)	7.18 (0.92-56.29)	40.87 (3.21-519.77)
ESSDAI ^b	-	-	1.92 (1.17-3.17)	1.86 (1.05-3.29)
SSDDI score	6.10 (1.19-31.19)	3.11 (1.49-6.47)	2.36 (1.39-4.00)	2.71 (1.37-5.35)
Asthma ^b	6.58 (1.31-33.11)	5.00 (0.76-33.14)	-	-
Rituximab ^b	11.86 (1.44-97.44)	112.63 (5.51-2,304.04)	-	-

^aVariables adjusted for sex, age, and disease duration.

^bLogistic regression model was not performed for ESSDAI with low C3 levels and asthma and rituximab with low C4 levels because there was no statistical significance in the bivariate analyses. CI: confidence interval; ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; OR: odds ratio; pSS: Primary Sjögren's syndrome; SSDDI: Sjögren's Syndrome Disease Damage Index.

cade is fundamental in the pathophysiology of asthma. On the contrary, patients with pSS may present with asthmatic symptoms that in many instances are secondary to small airway disease, frequently falsely interpreted as bronchial asthma (22, 23). Based on the cohort and case-control studies, small airway disease is the most common respiratory manifestation in pSS (22, 23). To the best of our knowledge, there are no previous studies evaluating the association of C3 hypocomplementemia in patients who have asthma and are suffering from pSS. We do not have an explanation for these results other than speculate that the association with C3 hypocomplementemia could be related to pSS and/or asthma itself; thus, further investigation is warranted.

As previously reported by our group, we found an association between C3 and C4 hypocomplementemia and damage accrual (4). Similarly, in a cohort study of Italian patients with pSS, low C4 levels were associated with systemic damage (24). In agreement with other studies, we also found that low C4 levels are associated with higher disease activity (25). Thus, our results confirm the prognostic value of these serologic markers in terms of disease activity and damage in pSS.

Our patients with low C3 levels were more likely to receive therapy with rituximab. This finding is expected because of the relationship of hypocomplementemia with interstitial lung disease. In a Spanish cohort of patients with pSS, more than 20% of patients with severe systemic disease received rituximab as an immunosuppressive treatment (26). Furthermore, in a French registry, researchers reported that rituximab was effective for patients with pSS presenting with systemic manifestations (27). Specifically, adequate clinical response was

observed in 78% of patients who presented with pulmonary involvement. Rituximab has been frequently used off-label in patients with rheumatic diseases complicated with interstitial lung disease, including pSS.

This study had some limitations that need to be highlighted. This was a cross-sectional study and we had to take into consideration the disadvantages inherent of its design. We had a small number of patients with pSS; consequently, the association with other manifestations that occur in a relatively low frequency could not be fully ascertained. For example, we could not confirm the relationship with lymphoma because in our study, only one patient had this lymphoproliferative disorder. The low number of patients also limited the multivariate analyses and induced large CIs. Our population had a relatively short disease duration (nearly 6 years); therefore, the association with comorbidities that occur in the long term, such as cardiovascular events, could not be determined. Additionally, disease activity was only evaluated at the study visit and not during the course of the disease. Finally, serum C3 and C4 levels were not measured throughout the disease course. We do not know if the immunomodulatory or immunosuppressive therapy would have an effect on these levels or if follow-up levels could be related or not with the clinical associations observed with hypocomplementemia at pSS diagnosis. Nonetheless, because C3 and C4 levels were measured at diagnosis before pSS therapy, they appear to have a prognostic value for the development of systemic involvement.

We conclude that patients with pSS presenting with low serum C3 and C4 levels at diagnosis may represent a subset of patients with a worse clinical outcome when compared with

those with normal complement levels. The patients who presented with low levels of C3 and C4 at diagnosis were more likely to have small vessel vasculitis and interstitial lung disease and had higher disease activity and damage accrual. Our results suggest that clinicians should evaluate serum C3 and C4 levels in patients with pSS to determine those at high risk for disease progression and damage.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (Approval Date: May 19, 2014; Approval Number: A6310114).

Informed Consent: Informed consent was not obtained due to the nature of this study.

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