The Association of Hypocomplementemia With Disease Activity in Patients With Primary Sjogren's Syndrome

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Abstract

We assessed the prevalence of hypocomplementemia (HC), possible risk factors, and its prognosis in patients with primary Sjögren's syndrome (pSS). The data of 84 patients with HC admitted in Hebei General Hospital were retrospectively analyzed and compared to data of patients with normocomplementemic (NC). Logistic regression analysis was used to detect risk factors. The presence of hyper-immunoglobulin G (IgG) and anti-Ro52 was significantly higher in patients with HC. The patients with pSS with HC had higher hematologic, renal, and nervous system involvement and The European League Against Rheumatism Sjögren's Syndrome Disease Activity Index score ($p < 0.05$) and received more immunosuppressant treatments than those with NC ($p < 0.05$). Multivariate logistic analysis indicated that renal involvement (odds ratio [OR] = 4.09), nervous system involvement (OR = 3.82), leukopenia (OR = 2.57), and hyper-IgG (OR = 3.34) were independent risk factors for pSS with HC. Thus, HC was not an uncommon manifestation of pSS and was associated with leukocytopenia, renal and nervous system involvement, and severe disease activity. HC occurred in younger and short-term patients with pSS. Those with pSS-HC had an increased possibility to develop systemic lupus erythematosus. Such patients have distinctive clinical manifestations and worse prognosis that require extensive treatments.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune rheumatic disease characterized by lymphocytic infiltration of exocrine glands, which could lead to heterogeneous and various clinical presentations from sicca symptoms to systemic disease[1]. Approximately one-third of patients with pSS present extra-glandular manifestations, and some of these symptoms (e.g., interstitial lung disease, central nervous system [CNS] disease, and renal tubular acidosis) are associated with increased mortality. Abnormal immune response of T and B cells[2–4], recognition of self-antigens (Ro/SSA, La/SSB, and others), and subsequent activation are crucial for the cascade of events leading to the pSS pathology development[5].

To date, there is increased evidence on distinct clinical phenotypes corresponding to unique autoantibodies. Various antibodies (e.g., anti-SSA, anti-SSB, anti-centromere antibodies [ACA]) have been reported to be classically correlated with parotid enlargement, Raynaud's disease, arthritis, vasculitis, renal tubular acidosis, peripheral neuropathy, and cytopenias[6–9]. Similarly, several serologic abnormalities, such as B-cell proliferation, present special clinical features; for instance, hypergammaglobulinemia is often accompanied by extraglandular manifestations, especially with cutaneous vasculitis and pulmonary, articular, and renal involvements[10–13]. To date, few studies have addressed the clinical manifestations of hypocomplementemia (HC) or prognostic factors. This condition is not frequently observed but reported as a prognostic marker for lymphoma development in patients with pSS[14,15].

Here, we described the clinical features and outcomes of patients with pSS with HC as the presenting feature. Our aim was to shed light on the frequency of HC in a cohort of patients with pSS and to evaluate which clinical and serological features are significantly associated with HC.

Results

Prevalence of HC in patients with pSS

The study cohort consisted of 333 patients (310 women and 23 men). The HC rate was 25.23% (84/333). Among the 84 patients with pSS with HC, 78 (92.86%) were women and 6 (7.14%) were men. Those with HC were younger than those without (49.86 ± 15.49 vs. 55.30 ± 12.38 years; p = 0.004).

Laboratory characteristics

As shown in Table 1, the patients with pSS with HC had striking significant differences between the two groups concerning the white blood cell (WBC) count ($p < 0.001$), in particular the neutrophil and lymphocyte counts ($p = 0.003$ and $p = 0.005$, respectively). The serum C-reactive protein (CRP) level was lower in patients with pSS-HC than in those with normal complement levels ($p < 0.001$), although the serum CRP level was approximately in a normal range. Additionally, the serum rheumatoid factor (RF) level (21.90 [10.6–158] vs. 16.55 [10.60–55.93]) was higher in the HC than in the normocomplementemic (NC) group, but the difference was not statistically significant ($p = 0.44$). Moreover, higher serum immunoglobulin G (IgG) levels were observed in the HC than in the NC group ($p < 0.001$). Further, higher serum IgG levels (53.57% vs. 30.04%, $p < 0.001$) and presence of anti-Ro52 positivity (71.43% vs. 56.22%, $p = 0.01$) were observed in patients with HC. Whereas, the positive rates of detecting antinuclear antibodies, ACA, anti-Ro/SSA, anti-La/SSB, and anti-RNP antibodies were not significantly different between the two groups. Besides, no significant difference in histologic evaluation of minor salivary gland, as a focus score ≥ 1, was observed between the two groups.

Table 1

Demographic and serological descriptors of patients with pSS with HC and NC

	HC group (n = 84)	NC group (n = 249)	p-value
Demographic features			
Sex (Women/Men)	13:1	13.65:1	0.92
Age at onset, years	49.86±15.49	55.30±12.38	0.004
Disease duration, months	24 [6–84]	60 [12–120]	0.004
Laboratory findings			
White blood cell count (×10^9/L)	4.52 [3.46–5.55]	5.12 [4.06–6.56]	0.001
Neutrophil counts (×10^9/L)	2.71 [2.02–3.60]	3.11 [2.23–4.41]	0.003
Lymphocyte counts (×10^9/L)	1.35 [0.98–1.72]	1.57 [1.18–1.90]	0.005
Hemoglobin (×g/L)	118.5 [107–127]	122 [111–134]	0.007
Platelet counts (×10^9/L)	199 [159.25–260]	228 [182–274]	0.006
ESR (mm/1 h)	15.5 [7–43]	19 [10–35]	0.27
CRP (mg/L)	1.27 [0.59–3.30]	3.3 [1.68–5.33]	<0.001
RF (IU/L)	21.90 [10.6–158]	16.55 [10.60–55.93]	0.44
IgG (g/L)	18.13 [13.16–25.50]	14.90 [12.20–18.13]	<0.001
IgA (g/L)	2.75 [1.80–3.90]	2.73 [2.02–3.55]	0.34
IgM (g/L)	1.12 [0.78–1.59]	1.18 [0.83–1.62]	0.48
Elevated ESR (n, %)	36/80, 45.00	115/241, 47.72	0.67
Elevated CRP (n, %)	8/76,10.53	55/238, 23.11	0.02
Hyper-IgG (n, %)	45/84, 53.57	73/243, 30.04	<0.001
RF (+) (n, %) *	40/78, 51.28	110/233, 47.21	0.45
ANA (+) (n, %) **	66, 78.57	197, 79.12	0.92
Anti-RNP (+) (n, %)	12, 14.29	27, 10.84	0.40
Anti-Ro52 (+) (n, %)	60, 71.43	140, 56.22	0.01
Anti-Ro/SSA (+) (n, %)	54, 64.29	133, 53.41	0.08

Anti-La/SSB (+) (n, %)	26, 30.95	53, 21.29	0.07
ACA (+) (n, %)	11, 13.10	34, 13.65	0.90
Pathological MSG with focus score ≥1 (n, %)	78/80, 97.50	231/243, 95.06	0.53

pSS, primary Sjögren's syndrome; RF, rheumatoid factor; ANA, antinuclear antibodies; MSG, minor salivary gland; ACA, anti-centromere antibodies; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; IgA, immunoglobulin A; IgG, immunoglobulin G; CRP, C-reactive protein; NC, normocomplementemic urticarial vasculitis; HC, hypocomplementemia

*positive RF > 20 IU/mL; **positive for ANA titers ≥ 1:320.

Clinical manifestations

In our study, the patients with pSS with HC more commonly exhibited hematological involvement (68.23% vs. 51.20%; p = 0.01), thrombocytopenia (11.76% vs. 4.03%; p = 0.01), and leukopenia (34.11% vs. 14.11%; p < 0.001) at pSS diagnosis (Table 2). Compared to patients with pSS-NC, the patients in the HC group presented higher renal (11.76% vs. 4.83%, p = 0.03) and nervous system involvement (18.82% vs. 10.08%, p = 0.03). There were no significant differences in the classic symptoms of sicca syndrome, such as xerostomia, xerophthalmia, and salivary gland enlargement (p = 0.66, p = 0.99, and p = 0.58, respectively). Meanwhile, although the difference was not statistically significant, the incidence of mucocutaneous involvement was higher (p = 0.19), whereas the frequencies of arthritis, pulmonary involvement, and lymphatic system involvement were lower (p = 0.11, p = 0.34, and p = 0.33, respectively) in patients with pSS with HC than in those with NC.

Table 2
Comparisons of disease activity measures between patients with pSS with low (HC) and normal (NC) complement levels

Variables (n/%)	HC group (n = 84)	NC group (n = 249)	p-value
Xerostomia	72, 85.88	218, 87.50	0.66
Xerophthalmia	62, 74.11	184, 73.79	0.99
Salivary gland enlargement	11, 14.11	27, 10.48	0.58
Hematological involvement	57, 68.23	128,51.20	0.01
Thrombocytopenia	10, 11.76	10, 4.03	0.01
Leukopenia	28, 34.11	36, 14.11	< 0.001
Lymphopenia	31, 36.47	57, 22.98	0.10
Arthritis	31, 36.47	115, 46.37	0.11
Pulmonary involvement	15, 17.64	56, 22.58	0.34
Renal involvement	10, 11.76	12, 4.83	0.03
Digestive involvement	6, 7.05	11, 4.43	0.39
Nervous system involvement	16, 18.82	25, 10.08	0.03
Mucocutaneous involvement	26, 30.58	59, 23.79	0.19
Raynaud's phenomenon	10, 11.76	28, 11.29	0.91
Lymphatic system involvement	6, 7.05	27, 10.88	0.33
ESSDAI	10.5 [6–15.5]	7 [3–12]	0.003

ESSDAI, European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; NC, normocomplementemic urticarial vasculitis; HC, hypocomplementemia; pSS, primary Sjögren's syndrome

Risk factors for HC in patients with pSS

Multivariate analysis confirmed that renal involvement (odds ratio [OR] = 4.09, 95% confidence interval [CI] 1.54–10.89, p = 0.005), nervous system involvement (OR = 3.82, 95% CI 1.76–8.27, p = 0.001), leukopenia (OR = 2.57, 95% CI 1.30–5.09, p = 0.007), and hyper-IgG (OR = 3.34, 95% CI 1.73–6.44, p < 0.001) were independent predictors of HC in patients with pSS (Table 3).

Table 3
Multivariate analysis of features predicting hypocomplementemia in patients with pSS

	p-value	OR	95% CI
Renal involvement	0.005	4.09	1.54–10.89
Nervous system involvement	0.001	3.82	1.76–8.27
Leukopenia	0.007	2.57	1.30–5.09
ACA positive	0.07	2.22	0.93–5.30
ANA positive	0.01	0.36	0.16–0.78
Hyper-IgG	< 0.001	3.34	1.73–6.44
CI, confidence interval; OR, odds ratio; pSS; primary Sjögren's syndrome; ANA, antinuclear antibodies;			
ACA, anti-centromere antibodies; IgG, immunoglobulin G			

Therapeutic regimens and follow-up examinations

In the pSS-HC group, 25 (29.76%) patients received oral prednisolone, while 89 (33.33%) received immunosuppressants, including cyclophosphamide (n = 1), cyclosporin A (n = 5), mycophenolate mofetil (n = 4), iguratimod (n = 3), leflunomide (n = 15), and hydroxychloroquine (n = 61). Moreover, 75 (89.29%) patients received prednisolone, immunosuppressants, or a combination of the aforementioned drugs. Compared with the patients with pSS-NC, those with pSS-HC required cyclosporin A (p = 0.03) and mycophenolate mofetil (p = 0.04) treatment. Over a median follow-up period of 31.68 (range, 21–49) months, four patients developed systemic lupus erythematosus (SLE), and no patients died.

Discussion

To our knowledge, this study included the largest cohort of patients with pSS with HC. Their demographic characteristics and treatment outcomes are presented (Table 1). Approximately, 25.33% of patients with pSS had HC, and were more likely to have decreased WBC counts compared with those with NC (4.51 vs. 5.12, p < 0.001). Additionally, we demonstrated that HC is a marker of disease activity when applied across the entire cohort of patients with pSS, as HC is associated with the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) score. However, to our knowledge, this is the first study to demonstrate that HC is a marker of pSS activity, thus suggesting the measurement of C3 and C4 levels to assess and monitor the condition of patients with pSS. Several candidates of risk factors in univariate analyses were found; of those, leukopenia, elevated IgG, renal involvement, and nervous system involvement were significantly related to HC development in patients with pSS, as observed in a multivariate analysis.

In this study, we found a prevalence of low C3 and C4 levels of 22.82% and 8.71%, respectively, which are similar to those of previous studies. Especially, Baldini et al.[16] detected low C3 and C4 levels in 15.3% and 11.1% of 1,115 patients, respectively. Jordán-González et al.[17] found low C3 and C4 levels in 9.57% and 13.83% of 94 patients, respectively, while Lin et al.[18] reported low C3 and C4 levels in 14.4% and 16.5% of their participants, respectively. The different ethnicity, cohort size, disease severity degrees, and cut-off levels of the complement assays used may be attributed to the different prevalence of HC observed in these studies. Therefore, these results suggested that complement consumption may contribute to the pSS etiopathogenesis.

Several previous studies have explored the potential role for abnormal complement activation in pSS. Especially, Zadura, et al. found that with the widespread autoantibody production, the C4BP levels decreased in parallel with the C3 and C4 levels in active patients with pSS, which suggested that disturbed complement regulation may contribute to pSS pathogenicity[19]. Interestingly, Sudzius et al. reported that the serum C4d level was significantly lower in anti-SSA/SSB Ab seropositive than in seronegative patients with pSS and was also correlated with the C4 and anti-SSB Ab levels and the κ/λ ratio. They proposed that the C4d level can be an appropriate marker of complement activation in patients with pSS with Abs[20]. Evans et al. reported the presence of positive staining for C9 around the tubular basement membranes in patients with pSS-TIN (Tubulointerstitial nephritis, TIN)[21]. Moreover, Xia et al. performed a retrospective study and investigated the prevalence and localization of C4d deposits in renal biopsy tissues of patients with pSS. They found that glomerular C4d deposition was observed in all patients with pSS-related membranous nephropathy (MN) and suggested a role for the mannan-binding lectin pathway of complement activation in patients with pSS-related MN[22]. With the evidence of the complement system *in vivo* activation, these results suggested that complement consumption affects pSS pathophysiology. Therefore, the presence of HC in patients with pSS may signify the presence of disease activity. This is consistent with our findings, which demonstrated a significant higher ESSDAI score in patients with pSS-HC.

Our main aim was to demonstrate the relationship of HC with its role in pSS and its prognostic parameters. Jordán-González1 et al. found that pSS patients with low C3 levels were more likely to have leukocytoclastic vasculitis (44.4% vs. 8.2%, p = 0.010) and interstitial lung disease (33.3% vs. 1.2%, p = 0.002) and be exposed to rituximab treatment (22.2% vs. 2.4%, p = 0.045) than those with normal C3 levels[17].

An increased interest in pSS-associated renal disease raised over the last few years. Specifically, the scientific interest focused on whether decreased complement in patients with pSS is associated with kidney involvement. In our study, HC was more commonly found in patients with renal disease than in those in other groups, which is in line with previous findings[23,24]. However, this finding was contradicted by other studies. Especially, Zhao et al. found that hypokalemic paralysis, assumed to be a surrogate of renal damage, did not show any association with low complement[25]. Moreover, Yang et al. published a retrospective study, which included 103 patients with pSS who had undergone kidney biopsy.

Interestingly, no significant differences were observed between patients with and without renal disease[26]. Combined with the pathological findings, it was suggested that complement activation may have contributed to Sjogren's nephritis development.

Nervous system involvement, ranging from the peripheral nervous system to the CNS, is known to be multifaceted and possibly underestimated in pSS. Neurological disease may arise many years before pSS diagnosis and was found to contribute to damage in patients with pSS. Our study is one of the first to report that nervous system involvement is a potential risk factor for HC in patients with pSS. Besides, we found that there was a relationship between the incidences of nervous system involvement and HC, which is consistent with the findings by Ye et al., who found that patients with pSS with neurological involvement showed reduced C3 levels ($p < 0.05$). Additionally, low C3 level was found to be a potential risk factor for neurological involvement in younger patients with pSS[27]. Moreover, arising data supported that the complement system may facilitate various neuroinflammation activities[28,29]. Because of the evidence indicating that the complement levels play key roles in driving multiple nervous pathologies, the complement system may be a potential therapeutic target for treating brain injury in patients with pSS[21,30].

The complement system plays a pivotal role in SLE development, and previous data reported that patients with pSS with low complement levels are more likely to develop SLE. In a retrospective study including 55 patients with Sjogren's syndrome-onset SLE (SS/SLE), Yunjiao et al. revealed that these patients showed a significantly higher frequency of low complement levels (C3, 54.5% vs. 12.7%; C4, 41.8% vs. 7.3%, $p = 0.000$). Additionally, low C3 and C4 levels were independent risk factors of SS/SLE development (low C3 levels, RR (Relative risk, RR) = 9.659, $p = 0.000$; low C4 levels, RR = 6.035, $p = 0.007$)[31]. In our study, four patients developed SLE during the follow-up period, which supported our notion that the patients with pSS with HC should be monitored carefully, as they are highly likely to develop SS/SLE.

Although the mechanisms underlying lymphoma pathogenesis in patients with pSS have not been well identified, low C3/C4 levels may help improve the survival of autoreactive B-cells in such patients and further, through mutations, increase the risk of lymphoid malignancy occurrence[32,33]. HC was thought to be associated with lymphoma development and worse prognosis in patients with pSS[14,16,34,35]. In our study, it is noteworthy that such patients with HC usually presented hypergammaglobulinemia, anemia, leukopenia, and, especially, lymphocytopenia at the time of pSS diagnosis, indicating that these conditions are strong predictors of lymphoma development. In accordance with previous reports, we confirmed the preponderance of high risk of lymphoma development in the HC group.

However, our study has several limitations. First, the study has a retrospective design. Second, we had no information regarding the cryoglobulin status. Especially, because of the lack of routine evaluation of cryoglobulin in our patients, we were unable to investigate their cryoglobulin status at the time of diagnosis. Therefore, we cannot exclude the possibility that patients with HC could also have cryoglobulinemia. To address this issue, a future study analyzing the predictive value of cryoglobulinemia

in Chinese patients with pSS is required. Third, in this study, potential clinical factors in estimating the prognosis, such as changes in the C3/C4 levels, were not well evaluated. Further prospective studies with a larger number of patients with pSS are needed.

In conclusion, we confirmed that low complement levels are associated with renal and neurologic manifestations in patients with pSS. It is noteworthy that such patients with HC usually presented hypergammaglobulinemia, anemia, leukopenia, and, especially, CD4 (+) lymphocytopenia at the time of pSS diagnosis, thus highlighting the increased risk of lymphoproliferative disease development. Furthermore, this study revealed that HC might help in the early identification of patients with pSS who need to receive more aggressive treatments. However, further large-scale prospective studies are needed to confirm these findings.

Methods

Patients

In total, the data of 333 patients with pSS who were admitted to Hebei General Hospital from January 2016 to March 2019 were retrospectively reviewed. All patients fulfilled the American-European Consensus Group 2002 revised classification criteria for pSS[36]. According to the presence of HC, our patients were divided into the study and control groups. The study was approved by the Research Ethics Committee of the Hebei General Hospital (NO.2016070), all patients provided written informed consent for all subjects.

Procedures

General data and laboratory and clinical information at onset of patients with pSS were retrospectively reviewed, including the first presentation and systemic involvements. Clinical data, such as age at diagnosis, disease duration, oral and ocular dryness, and constitutional symptoms, as well as data on joint, pulmonary, kidney, vasculitis, skin, nervous, gastrointestinal tract, and endocrine involvement were collected. The levels of complements (C3 and C4), erythrocyte sedimentation rate, CRP, immunoglobulins (IgG, IgM, and IgA), RF, anti-SSA, and anti-SSB were retrieved from the case records. The laboratory tests were performed at the regular hospital laboratory. The disease activity was determined according to the 2010 ESSDAI[37,38]. All of the tests were performed at the clinical laboratory and all methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

All data were analyzed using a standard statistical package (SPSS for Windows, version 25.0; IBM Corp., Armonk, NY, USA). Data are presented as means ± standard deviations, medians and interquartile ranges, or percentage frequencies, as appropriate. Group comparisons were conducted by Student's t-test, Mann–Whitney's U-test, or Fisher's exact test, as appropriate. The potential risk factors for HC were assessed by

multiple logistic regression analysis, and the results are expressed as ORs and 95% CIs. The level of significance was set at $p < 0.05$.

Declarations

Data availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Conception and design: LW, ZF, ZW; acquisition of data: XZ, NX, YL, GS; analysis and interpretation of data: LY, NX, LM, SY; statistical analysis: LY, LW; drafting the article or revising it critically for important intellectual content: all authors; final approval of the version published: all authors;

Competing interests

All authors declare that they have no conflict of interest.

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