Original Article

Clinical and laboratory features of primary Sjögren's syndrome complicated with mild to severe thrombocytopenia

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Background: Patients with thrombocytopenia accompanied by positive Ro/SS-A and/or La/SS-B autoantibodies have a possible diagnosis of Sjögren's syndrome (SS). Owing to its low prevalence, large-sample controlled studies on thrombocytopenia in primary SS (pSS) are scarce. Thus, this study aimed to investigate the clinical and laboratory characteristics of pSS complicated with mild to severe thrombocytopenia, and compared them with pSS patients without thrombocytopenia.

Methods: This medical records review study analyzed the demographic data, clinical manifestations, laboratory examinations, and other results of 88 patients diagnosed with pSS between March 2007 and March 2018 in the Department of Rheumatology of The First Affiliated Hospital of Soochow University. A platelet (PLT) count of peripheral blood below 50×10^9/L ($\leq50\times10^9$/L) was regarded as mild to severe thrombocytopenia.

Results: Of the 88 pSS patients, 43 developed mild to severe thrombocytopenia (thrombocytopenia group) and 45 had no thrombocytopenia (control group). No significant difference was found in the levels of autoantibodies and inflammatory markers between the thrombocytopenia group and the control group. Dry mouth ($P<0.01$) and dry eyes ($P<0.01$) were not frequently observed in the thrombocytopenia group, but the level of complement C4 dropped significantly ($P<0.05$). In contrast, the control group was more likely to have leukopenia ($P=0.01$) and interstitial lung disease ($P<0.01$).

Conclusions: In pSS patients with mild to severe thrombocytopenia, the incidence of xerostomia, xerophthalmia, and lung involvement was markedly reduced. Knowledge about the features of pSS associated with thrombocytopenia will lead to earlier and better diagnosis and treatment.

Keywords: Primary Sjögren's syndrome (pSS); thrombocytopenia; lung involvement

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Introduction

Sjögren's syndrome (SS; also known as Sicca syndrome) is a chronic systemic autoimmune disease characterized by xerophthalmia (dry eyes) and/or xerostomia (dry mouth). Glandular features such as dry eyes and dry mouth can also occur as a late complication in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other rheumatic disorders, called 'secondary' SS (1).

In addition to the impaired function of exocrine glands, other organs may be also involved, such as the skin, joints, lungs, liver, kidneys, and hematological system.

Hematologic abnormalities is common in primary SS (pSS) patients, a third of patients with SS have cytopenias such as leukopenia, anemia, and thrombocytopenia (2), because its degree is usually mild and asymptomatic, often have been disregarded in daily practice and only a few studies conducted on it. Leukopenia occur in about 20–60% of patients, associated with positive anti-SSA antibodies and a more severe glandular involvement (3-5). Anemia is also frequently seen in pSS, its reported that anemia occurs in 11.2–19% of pSS patients (6), but autoimmune hemolytic anemia (AIHA) is uncommon in pSS. In a study, the pSS patients with AIHA, fever, liver involvement, leukopenia and thrombocytopenia occurred significantly more frequently than those without AIHA (7). Although in pSS, leukopenia and anemia is the most common complications of the hematological system, a few cases are complicated with AIHA and thrombocytopenia (8). A previous study analyzed 99 pSS patients and reported that 61 (61.5%) developed lymphopenia and leukopenia, and 7 (7.1%) had thrombocytopenia (9).

Although thrombocytopenia is not common in pSS patients (10), severe thrombocytopenia can increase the occurrence of adverse events, which are sometimes fatal. Some patients are misdiagnosed because they lack the typical signs in their eyes and mouths (11). Thus, in 2015, the European League Against Rheumatism (EULAR) has promoted and supported an international collaborative study group (EULAR-SS Task Force) that is aimed at developing consensual recommendations to provide a homogeneous approach to pSS patients presenting with systemic involvement. The guideline mentioned that patients with thrombocytopenia accompanied by positive Ro/SS-A and/or La/SS-B autoantibodies have a possible diagnosis of SS (12). Due to its low prevalence, large-sample controlled studies on thrombocytopenia in pSS are scarce. Thus, in this study, we aimed to investigate the clinical and laboratory characteristics of pSS complicated with mild to severe thrombocytopenia, and compared them with those of pSS patients without thrombocytopenia. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-162/rc).

Methods

Design

In this medical records review study, we identified 841 pSS patients hospitalized in the Department of Rheumatology of The First Affiliated Hospital of Soochow University between March 2007 and March 2018. Of these pSS patients, 43 developed mild to severe thrombocytopenia (thrombocytopenia group), and 45 patients who did not develop thrombocytopenia were included in the analysis as the control group. The age and sex of the control group were matched to those of the thrombocytopenia group. The patients' demographic data, clinical manifestations, laboratory examinations, and other results were analyzed retrospectively.

Patients

PSS diagnosis was confirmed either by pathological or clinical methods based on the 2002 American College of Rheumatology Classification Criteria (13). Patients with other diseases such as chronic hepatitis C, human immunodeficiency virus infection, previous lymphoproliferative processes, or other autoimmune diseases were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Board of The First Affiliated Hospital of Soochow University (No. 2020105). Individual consent for this retrospective analysis was waived.

Clinical features

The clinical characteristics of pSS are as follows: fever, axillary temperature >37.5 ℃; Raynaud phenomenon, cool skin and cutaneous color changes of the fingers and toes exposed to cold and/or stress; articular features, arthralgia or non-erosive arthritis involving two or more peripheral joints; pulmonary complications, chronic and persistent cough, dyspnea, or both, with alveolitis or fibrosis in computed tomography (CT) scans; nephropathy, permanent proteinuria (>0.5 g/day), continuously increasing serum creatinine (Cr) level (>111 μmol/L), renal tubular acidosis, or glomerular nephritis; liver damage, altered plasma liver function (aminotransferase, alkaline phosphatase, gamma glutamyl transferase, and bilirubin) and/or altered bile ducts in ultrasonography, CT, or magnetic resonance imaging; hemorrhagic manifestations, skin bleeding (skin purpura or bruises), oral bleeding (oral blood blister or gingival bleeding), nasal hemorrhage, gastrointestinal bleeding (visible bleeding or fecal occult blood), urinary bleeding (urinating blood or microscopic hematuria), vaginal bleeding (massive bleeding or prolonged menstrual period), conjunctival bleeding, and intracerebral hemorrhage.

Table 1 Characteristics of pSS patients with or without mild to severe thrombocytopenia

Parameters	pSS with mild to severe thrombocytopenia (n=43)	pSS without thrombocytopenia (n=45)	P value
Female, frequency (%)	95.3 (40/43)	95.6 (43/45)	0.670
Age (years), mean ± SD	51.69±12.43	41.46 ±14.89	0.429
Disease duration (months), IQR	18	44	0.216
ESSDAI score, mean ± SD	4.63±1.36	3.24±1.96	<0.001**
Average hospital stay (days), mean ± SD	14.00±6.98	10.53±6.01	0.002**

**P<0.01. pSS, primary Sjögren's syndrome; SD, standard deviation; IQR, interquartile range; ESSDAI score, EULAR Sjögren's syndrome disease activity index.

The seriousness of bleeding was assessed using the immune thrombocytopenic purpura (ITP) bleeding scoring system (14).

Laboratory features

The laboratory features were as follows: mild to severe thrombocytopenia manifested by platelet (PLT) count $<50\times10^9$/L, leukopenia as leucocyte count $<4.0\times10^9$/L, anemia as hemoglobin (HGB) <120 g/L, and hypocomplementemia with complement 3 (C3) <0.79 g/L and/or complement 4 (C4) <0.16 g/L. Rheumatoid factor (RF) (latex test positive at a value >20 IU/mL) was analyzed by enzyme-linked immunosorbent assay. Antinuclear antibodies (ANAs; positive at a titer 1:100 by indirect immunofluorescence) and 60- and 52-kDa forms of anti-Ro/SSA and anti-La/SSB antibodies were tested independently.

Statistical analysis

SPSS software version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables were compared using the Wilcoxon test, and proportions were analyzed using chi-square and Fisher's exact test. P<0.05 was considered to indicate statistical significance.

Results

Patient characteristics

In this study, the total incidence rate of mild to severe thrombocytopenia in pSS patients was 5.1%. Among the 43 patients with mild to severe thrombocytopenia, only 3 (6.9%) were men. PSS patients with mild to severe thrombocytopenia were 17–70 years old, with a mean age of 51.69±12.43 years, while control patients were 41.46±14.89 years old. The median disease duration in the thrombocytopenia group was 18 *vs.* 44 months in the control group (*Table 1*).

Clinical features in pSS patients with mild to severe thrombocytopenia

Table 2 presents the clinical features of patients in the thrombocytopenia group. The classic manifestations of SS, such as dryness of the mouth and eyes, rampant caries, and other clinical features like fatigue, fever, and weight loss were observed. The incidence rates of xerostomia and xerophthalmia were significantly lower in the thrombocytopenia group than in the control group (P=0.0028, and P=0.0024, respectively). Of the 43 patients in the thrombocytopenia group, 17 sought admission because of thrombocytopenia and/or hemorrhagic manifestations, without exocrine gland features. Meanwhile, pulmonary interstitial disorders were more common in the control group (P=0.0088). There were no statistically significant differences in the frequency of fever, rashes, arthritis, and Raynaud phenomenon between the two groups. As expected, the thrombocytopenia group had a significantly higher EULAR Sjögren's syndrome disease activity index (ESSDAI scores) than the control group (P<0.001).

Differences in serologic features

Not surprisingly, the PLT count in the thrombocytopenia group was markedly lower than that in the control group (P<0.001). The thrombocytopenia group had significant hypocomplementemia (C4 level) compared to the control group (P=0.0024). However, the existence of ANA, anti-SSA 60- and 52-kDa, anti-SSB, M2, anti-double-stranded DNA (anti-dsDNA), and anti-centromere antibodies (ACAs)

Table 2 Clinical features in pSS patients with or without mild to severe thrombocytopenia

Symptoms	pSS with mild to severe thrombocytopenia, n (%)	pSS without thrombocytopenia, n (%)	P value
Xerophthalmia	26 (60.5)	40 (93.0)	0.003**
Xerostomia	17 (39.5)	33 (73.3)	0.002**
Rampant caries	14 (32.5)	19 (42.2)	0.385
Salivary gland enlargement	1 (2.3)	3 (6.6)	<0.001**
Fever	0 (0.0)	3 (6.6)	0.242
Rash	3 (6.9)	10 (22.2)	0.069
Arthralgia	11 (25.6)	16 (35.5)	0.360
Lung involvement	4 (9.3)	15 (33.3)	0.009**
Liver involvement	4 (9.3)	2 (4.4)	0.428
Renal involvement	3 (6.9)	4 (8.9)	0.742

**P<0.01. pSS, primary Sjögren's syndrome.

Table 3 Serological clinical features and antibody expression in pSS patients with or without mild to severe thrombocytopenia

Parameters	pSS with mild to severe thrombocytopenia, n (%)	pSS without thrombocytopenia, n (%)	P value
Leukopenia	7 (16.3)	19 (42.2)	0.010**
Anemia	14 (32.5)	8 (17.8)	0.141
Hypocomplementemia	25 (58.1)	27 (60.0)	0.180
ANA	41 (95.3)	39 (86.7)	0.270
Anti-SSA 52-kDa	39 (90.7)	40 (93.0)	0.781
Anti-SSA 60-kDa	30 (69.7)	39 (86.7)	0.070
Anti-SSB	27 (62.8)	33 (73.3)	0.362
M2	4 (9.3)	5 (11.1)	0.781
Anti-dsDNA	4 (9.3)	1 (2.2)	0.197
U1RNP	2 (4.6)	2 (4.4)	0.963
CENPB	2 (4.6)	4 (8.9)	0.677
ACA	2 (4.6)	1 (2.2)	0.612

**P<0.01. pSS, primary Sjögren's syndrome; ANA, antinuclear antibody; dsDNA, double-stranded DNA; ACA, anti-centromere antibody.

was not obviously different between the two groups (*Table 3*). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and RF were not markedly different between the two groups. The levels of immunoglobulin A (IgA) were significantly lower in the thrombocytopenia group than in the control group (P=0.0019); however, no difference was observed between the levels of IgG and IgM in the two groups. Among the regular chemical parameters, the glutamic-pyruvic transaminase (alanine transaminase) level was significantly increased in the thrombocytopenia group (P=0.043) (*Table 4*).

Disease and prognosis in pSS patients with mild to severe thrombocytopenia

In the thrombocytopenia group, the most common hemorrhagic manifestations were skin bleeding, such as purpura/bruises (21 of 43, 48.8%), and gingival bleeding

Table 4 Serologic features in pSS patients with or without mild to severe thrombocytopenia

Parameters	pSS with mild to severe thrombocytopenia (n=43), mean ± SD	pSS without thrombocytopenia (n=45), mean ± SD	P value
WBC ($\times10^9$/L)	7.20±3.37	4.7±2.00	<0.0001**
HGB (g/L)	111.79±27.41	120.18±20.48	0.066
PLT ($\times10^9$/L)	29.72±15.44	203.82±65.44	<0.0001**
RF (IU/mL)	103.52±146.22	172.23±375.29	0.832
ESR (mm/h)	33.36±30.52	36.59±24.74	0.350
CRP (mg/L)	5.32±6.70	4.75±6.38	0.738
C3 (g/L)	0.82±0.22	0.83±0.23	0.847
C4 (g/L)	0.16±0.06	0.18±0.06	0.024*
IgA (g/L)	2.81±1.30	3.63±1.43	0.019*
IgG (g/L)	19.34±6.60	17.55±5.56	0.269
IgM (g/L)	1.53±0.76	1.39±0.80	0.193
ALT (U/L)	31.82±38.69	19.52±15.18	0.043*
AST (U/L)	24.12±12.31	22.99±10.13	0.919
BUN (mmol/L)	5.37±2.19	4.75±1.54	0.408
Cr (μmol/L)	54.14±12.22	56.90±10.17	0.267

*P<0.05; **P<0.01. pSS, primary Sjögren's syndrome; SD, standard deviation; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; C3, complement 3; C4, complement 4; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM immunoglobulin M; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cr, creatinine.

Table 5 Characteristics of pSS patients with mild to severe thrombocytopenia

Parameters	pSS with mild to severe thrombocytopenia
Haemorrhagic manifestations, n (%)	29 (67.4)
Skin purpura/bruises, n (%)	21 (48.8)
Gingival bleeding, n (%)	17 (39.5)
Epistaxis, n (%)	6 (13.9)
Hemoptysis, n (%)	0 (0.0)
Hematuria, n (%)	1 (2.3)
Hematochezia, n (%)	7 (16.3)
Vaginal bleeding, n (%)	7 (16.3)
ITP bleeding scores, mean ± SD	1.32±1.17
PLT (before the treatment), mean ± SD	29.72±15.44
PLT (after the treatment), mean ± SD	138.32±94.65
Treatment effective, n (%)	35 (81.4)

pSS, primary Sjögren's syndrome; ITP, immune thrombocytopenic purpura; SD, standard deviation; PLT, platelet.

(17 of 43, 39.5%). There were no hemorrhagic manifestations in 14 of 43 patients (32.6%) (*Table 4*). At baseline, the ITP bleeding score was 1.32±1.17, and no correlation was found between hemorrhagic manifestations and treatment effect (*Table 5*). No patient died during the study period. Mild to severe thrombocytopenia was treated with high-dose corticosteroids and/or intravenous gamma-immunoglobulin, and hydroxychloroquine and cyclosporine were also used. During hospitalization, 35 of the 43 patients were responsive to treatment, while the remaining eight patients were not. One patient underwent splenectomy because of refractory thrombocytopenia.

Discussion

To the best of our knowledge, this is the first study to demonstrate a negative correlation between mild to severe thrombocytopenia and lung involvement in pSS. PSS is one of the major chronic inflammatory autoimmune diseases associated with B lymphocyte hyper-reactivity. Recently, the prevalence of pSS has been reported to range from 0.05%

to 0.23% (15,16), and in China, the prevalence of pSS is approximately 0.33–0.77% (17). Although most patients have exocrine gland involvement, such as labial gland and lacrimal gland involvement (18), their clinical manifestation is usually quite non-specific and varied, resulting in delayed diagnosis for 3–8 years from the onset of first symptoms (19,20). In our study, all 88 patients received pathological examination of lower lip biopsy. Among the pSS patients with mild to severe thrombocytopenia, four had no lymphocytic foci; however, in pSS patients without thrombocytopenia, one had no lymphocytic foci.

The mechanisms of SS with thrombocytopenia is not clear. A few studies have shown that may be a complex immune pathology relating multiple factors, such as P-selectin (21), TLR7 signaling pathway (22) and FcγRIIb on B cells (23).

A multicentre study reported a 3.7% incidence of thrombocytopenia in patients with SS (4). In our study, 5.1% of pSS patients developed mild to severe thrombocytopenia, and among these patients, 95.3% were female. Moreover, our participants were in-patients, making our cohort similar to those in other studies. Previous studies have reported that 5–16% of pSS patients develop thrombocytopenia (17,24,25). Although there was no real distinction in the median time for diagnosis confirmation between patients with or without mild to severe thrombocytopenia, pSS patients with mild to severe thrombocytopenia had obviously higher ESSDAI scores than those without, and required longer hospitalization.

Leukopenia is the most frequent hematologic abnormality noted in pSS, and 30–40% of pSS patients may have leukopenia (8). In our study, 29.5% of patients had leukopenia, but among patients with mild to severe thrombocytopenia, the prevalence of leukopenia was significantly lower than in those without thrombocytopenia. All patients responded remarkably well to corticosteroids. Anti-neutrophil antibody may be responsible for autoimmune neutropenia (26), but the low frequency of neutropenia in pSS patients with mild to severe thrombocytopenia was not reported in previous studies; thus, further research is required. In our study, decreased levels of C4 and IgA were more common in the thrombocytopenia group, indicating a possible important complex immune mechanism in the pathogenesis of thrombocytopenia in pSS patients.

A large proportion of patients in both groups were positive for ANA. The prevalence of all autoantibodies such as anti-SSA and anti-SSB, AIM-M2, CENPB, ACA, anti-dsDNA, and U1RNP showed no remarkable differences between the two groups. For some antibodies, the absence of a significant difference may have resulted from a relatively small sample size.

Lung involvement is present in 10–20% of pSS patients (27). Among 88 patients, 21.6% had lung involvement, which fairly accorded with the results in previous study (28). The prevalence of pSS-ILD is around 20% in pSS patients (29). PSS-ILD can occur at any stage in the course, and the severity of pSS-ILD do not correlate with the manifestations of pSS. The common ILD pattern is nonspecific interstitial pneumonia, usual interstitial pneumonia and organising pneumonia, lymphocytic interstitial pneumonia in SS patients. However, in pSS patients with mild to severe thrombocytopenia, the incidence of lung involvement reduced markedly in our study. PLT-derived growth factor was reported to contribute directly to the migration of fibrocytes to the injured lungs (30). The current understanding of the pathophysiology of lung disease in pSS suggests a similar process as those in the salivary glands, with epithelial cells playing a critical role in the initiation (28). It can be assumed that pSS with lung involvement and pSS with hematological involvement have different pathological and clinical manifestations. This study has limitations that hindered the generalization of the results, including the small sample size, retrospective design, and single-center setting, etc. Thus, more research is needed on the relationship between thrombocytopenia and lung involvement in pSS.

There's no report on the recurrence rate of thrombocytopenia in patients with pSS. The same thing happened in primary immune thrombocytopenia (ITP). Antibodies against PLT glycoproteins and inflammation has been shown to be closely related to the pathogenesis and prognosis of ITP (31). Therefore, close follow-up and avoidance of infection may be an effective way to prevent recurrence.

In conclusion, our study explored the clinical features of pSS accompanied by mild to severe thrombocytopenia. PSS patients with mild to severe thrombocytopenia could have higher ESSDAI scores than those without thrombocytopenia, but the incidence of some complications such as leukopenia and lung involvement was low. In pSS patients with mild to severe thrombocytopenia, the incidence of xerostomia, xerophthalmia, and lung involvement was markedly reduced. Thrombocytopenia could be present upon the onset of pSS development, without any involvement of the exocrine glands. Thus,

there is an urgent need for more detailed classification of pSS based on its clinical manifestations and pathology. Knowledge about the features of pSS associated with thrombocytopenia will lead to earlier and better diagnosis and treatment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Board of The First Affiliated Hospital of Soochow University (No. 2020105). Individual consent for this retrospective analysis was waived.

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