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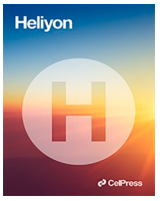

Case report

Association of Sjögren's syndrome with immune-mediated thrombotic thrombocytopenic purpura and posterior reversible encephalopathy syndrome: A case report

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ABSTRACT

Background: A patient with Sjögren's syndrome (SS), immune-mediated thrombotic thrombocytopenic purpura (ITTP), and posterior reversible encephalopathy syndrome (PRES) was reported, and all published cases with thrombotic thrombocytopenic purpura (TTP), PRES, and SS were retrieved and analysed. The patient's clinical data and treatment procedure have been discussed. *Case summary:* A 45-year-old Chinese female was hospitalized with headache and low platelet count. She had previously presented to a local hospital with a 7-month history of epigastric discomfort and anorexia, and was diagnosed with SS and ITTP. Laboratory investigations after admission showed platelet (PLT) of 13*10^9/L, red blood cell (RBC) fragments of 6 %, ADAMTS13 Activity < 0.2 %, anti-ADAMTS13 IgG of 88.3U/mL. Brain magnetic resonance imaging (MRI) showed gyriform restricted diffusion along with increased T2-FLAIR signal in the left frontal cortex and bilateral parietal temporal cortex. She was diagnosed with SS, ITTP and PRES, and received the treatment of methylprednisolone, cyclosporine, plasma exchange, IVIG, and rituximab. This patient did not experience the recurrence during the 8-month follow-up period. *Conclusion:* ITTP and PRES are rare manifestations of SS. After a suspected or confirmed diagnosis of ITTP, plasma exchange and immunosuppressive therapy should be immediately administered. We suggest that rituximab could have additional therapeutic value for SS combined with ITTP and PRES.

1. Introduction

Primary Sjögren's syndrome (PSS) is a type of systemic autoimmune disease which is featured by lymphocytic infiltration of the secretory glands. This process results in sicca syndrome, manifested by the dryness of eyes, oral cavity, pharynx, larynx, and vagina. It had extraglandular manifestations: cutaneous, musculoskeletal, pulmonary, renal, haematological, and neurological involvement [1]. Thrombotic thrombocytopenic purpura (TTP), a thrombotic microangiopathy, is unusual and life-threatening, and it is particularly associated with severe ADAMTS13 deficiency. ADAMTS13 deficiency is commonly caused by ADAMTS13 autoantibodies; and it, however, is hardly inherited by the *ADAMTS13* gene mutations. Usually, the first onset of TTP happened in adulthood, which is predominantly caused by anti-ADAMTS13 autoimmune deficiency [2]. The treatment modalities consisted of plasma exchange,

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corticosteroids and other immunosuppressants. A few patients of TTP are refractory, and require additional therapies such as rituximab, bortezomib, and cyclosporine [2]. Posterior reversible encephalopathy syndrome (PRES) is an acute- or subacute-onset neurological disease, which is characterised by various clinical neurological manifestations, including headache, epileptic seizures, altered consciousness, impaired vision (vision loss most commonly happening), altered mentation, and focal neurological deficits [3]. These conditions are caused by hypertension, immune diseases, and drug use. Although rare, PRES can occur simultaneously with TTP during the progression of autoimmune disease. In this case-based review, a 45-year-old female patient with Sjögren's syndrome (SS), refractory immune-mediated TTP (ITTP) and PRES, was reported, who received the treatment of methylprednisolone, cyclosporine, plasma exchange, intravenous immunoglobulin (IVIG), and rituximab. This patient did not experience the recurrence during the 8-month follow-up period. Furthermore, we extensively reviewed the literature on SS, TTP, and PRES.

2. CASE presentation

2.1. Chief complaints

A 45-year-old Chinese female, with a low platelet count for more than 6 months and headache for 6 days, was hospitalized in the Qianfoshan Hospital.

2.2. History of present illness

The patient had previously presented to a local hospital with a 7-month history of epigastric discomfort and anorexia, and was diagnosed with SS (dry mouth, dry eyes, positive Schirmer test, anti-SSA antibody-positive, and anti-SSB antibody-positive) and ITTP. After treated with methylprednisolone and recombinant human thrombopoietin injection (rhTPO), the patient was discharged after the improvement of his condition. However, the patient was subsequently admitted to the hospital twice because of anaemia and platelet decrease, for which she received methylprednisolone, vincristine, and rhTPO.

2.3. Personal and family history

The personal and family histories were normal.

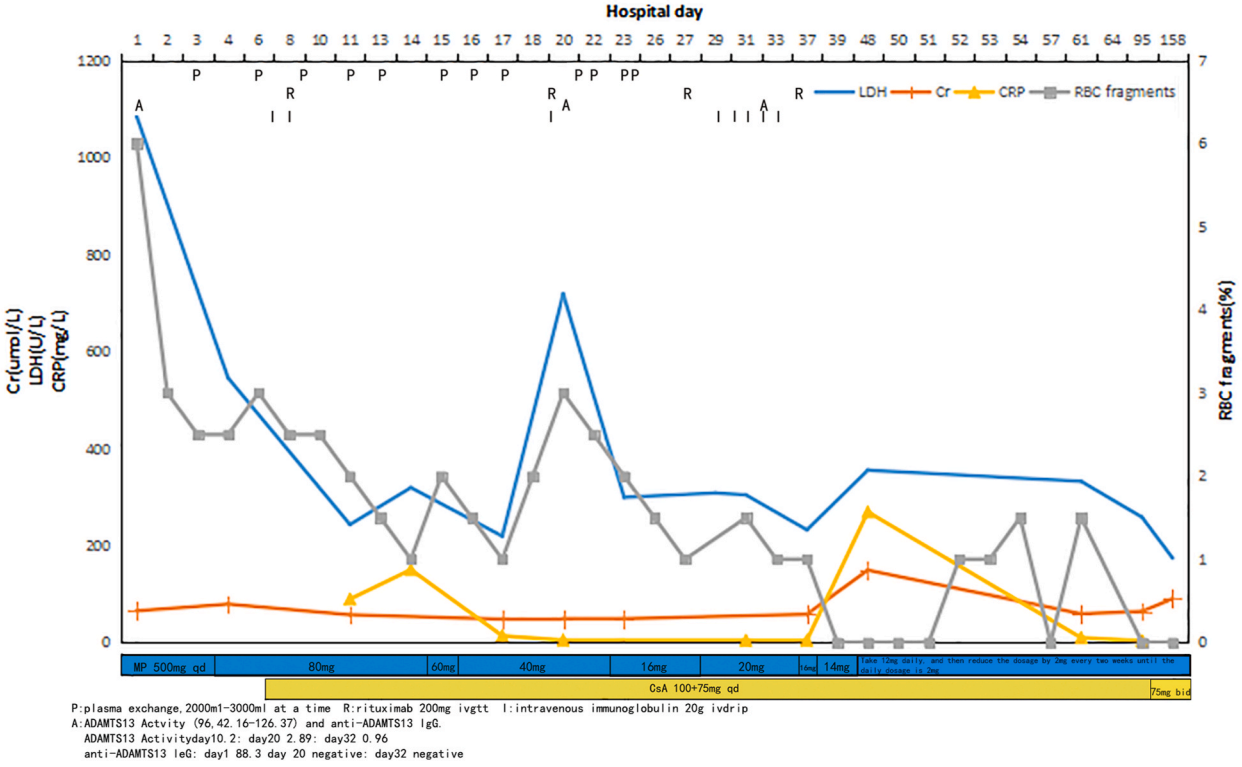

Fig. 1. Changes in the levels of CRP, Cr, LDH, RBC fragments and treatment interventions during hospital course.

2.4. Physical examinations

Physical examination revealed rampant caries and scattered ecchymosis in the limbs. With the progression of diseases, new symptoms developed, including intermittent slurring of speech, 4-grade muscle strength of the left upper limb, and excessive vaginal bleeding.

3. Laboratory examinations

Routine blood test showed white blood counts (WBC) of 6.89*10^9/L, red blood cell (RBC) of 1.91*10^12/L, haemoglobin (HGB) of 66 g/L, platelet (PLT) of 13*10^9/L, Coombs test with negative results, RBC fragments of 6 %, ADAMTS13 Activity < 0.2 %, and anti-ADAMTS13 IgG of 88.3U/mL (Figs. 1 and 2). Antinuclear antibody (ANA) of 1:1280, anti-SSA antibody-positive, and anti-SSB antibody-positive were showed.

3.1. Imaging examinations

Brain magnetic resonance imaging (MRI) showed gyriform restricted diffusion along with the increased T2-FLAIR signal in the left frontal cortex and bilateral parietal temporal cortex.

4. Final diagnosis

The condition was diagnosed as SS, ITTP and PRES based on the above physical examinations, laboratory examinations, and imaging data.

5. Treatment

After the treatment with 40 mg of dexamethasone, rhTPO, and one unit of platelets, the patient's symptoms did not improve; and additionally, new symptoms developed, including intermittent slurring of speech, impaired movement of the left upper limb, and excessive vaginal bleeding. Routine blood test showed WBC of 6.89*10^9/L, RBC of 1.91*10^12/L, HGB of 66 g/L, and PLT of 13*10^9/L, and Coombs test was negative. Considering the patient's medical history, the patient was referred to the rheumatology department for continued treatment after consultation. We further improved the relevant inspections, such as routine blood test, liver and kidney function tests, schistocyte estimation, on February 10, 2023 (Figs. 1 and 2). Because the patient developed headaches and confusion, we performed brain MRI, which showed gyriform restricted diffusion along with the increased T2-FLAIR signal in the left frontal cortex

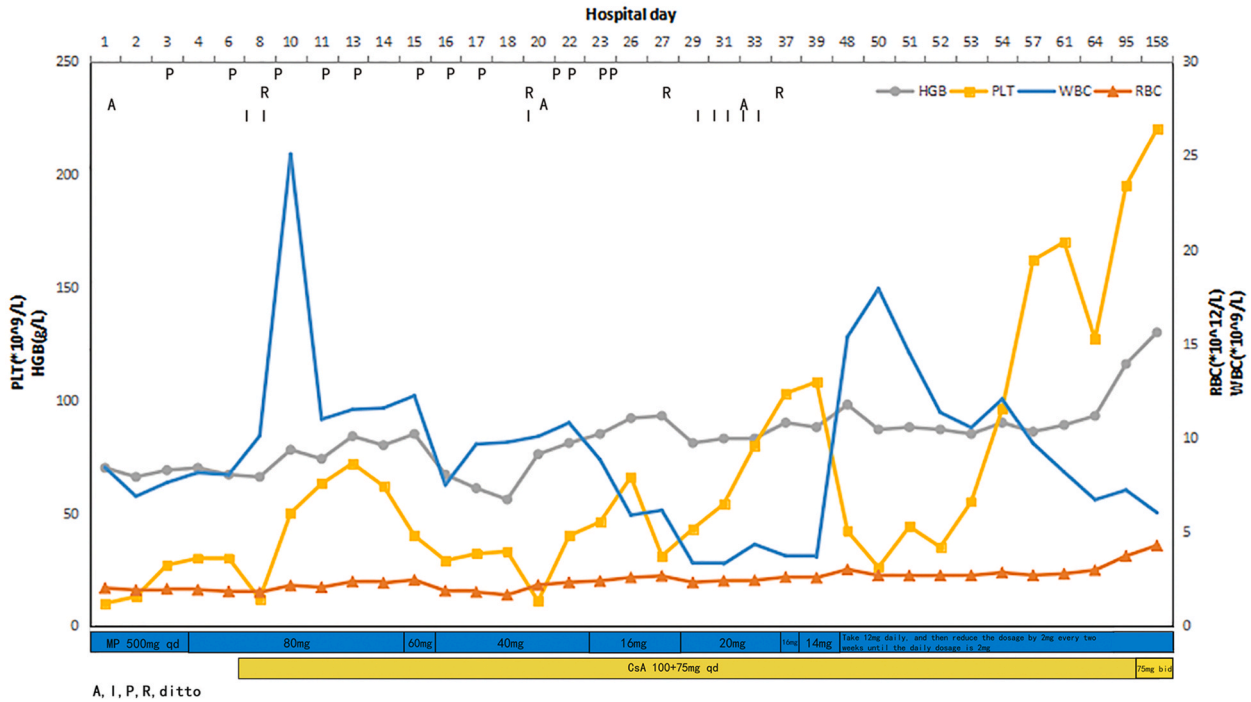

Fig. 2. Changes in WBC, RBC, HGB, PLT, and treatment interventions during the hospital stay.

and bilateral parietal temporal cortex. We repeated the ADAMTS13 activity and inhibitor tests, and obtained results after seven days (Figs. 1 and 2). Based on the combination of findings and clinical manifestations, we considered a possible diagnosis of SS associated with ITTP and PRES, and the patient received plasma exchange before obtaining the ADAMTS13 results. It was unable to exchange plasma 1–2 times daily because of a lack of plasma supply (Figs. 1 and 2). After treatment with methylprednisolone, cyclosporine, plasma exchange, and IVIG (Figs. 1 and 2), the patient's overall condition and neurological symptoms improved. However, the patient's relevant indicators did not return to normal (RBC fragments, HGB, and PLT; Figs. 1 and 2). Based on the patient's clinical condition, rituximab was intravenously administered weekly at a dose of 200 mg. The patient experienced fever and chills due to the contamination of the indwelling catheter, which was used for plasma exchange; and then the symptoms resolved after receiving targeted antibiotic therapy. After four administrations of rituximab, the relevant indicators improved (Figs. 1 and 2). In the subsequent treatments, the doses of methylprednisolone and cyclosporine were gradually reduced.

6. Outcome and follow-up

Subsequent brain MRI revealed scattered ischaemic foci. The patient recovered without any relapse during the follow-up period of 8 months.

7. Discussion

After reviewing the literature, 20 patients with SS and TTP in 17 studies were identified, and two articles reported two patients with SS, TTP, and PRES. Table 1 summarises our case report and the published cases with SS, TTP and PRES [4–19]. Most patients were female (17/20, 85 %), with age ranging from nineteen to seventy-five years old. The order disease appeared was as follows: SS was present before TTP in 11 cases, TTP was present before SS in 4 patients, and both diseases occurred simultaneously in 5 patients. PSS (no other immune diseases) in 17/20 (85 %) cases, and secondary SS was observed in 3/20 (15 %) cases: rheumatoid arthritis (n = 1), COVID-19 (n = 1), and dermatomyositis (n = 1). Anaemia and thrombocytopenia were observed in 20/20 (100 %) cases, consciousness alteration in 15/20 (75 %) cases, schistocytes in 13/20 (65 %) cases, renal impairment in 10/20 (50 %) cases, fever in 9/20 (45 %) cases, and headache in 8/20 (40 %) cases. The distributions of SS-related autoantibodies were: ANA of 15 patients, anti-Ro/SS-A of 17 patients, anti-La/SS-B of 10 patients, and rheumatoid factor of 1 patient. Refractory TTP was observed in seven patients, of whom 5 patients recovered (three patients treated with rituximab, one with bortezomib, and one with cyclophosphamide), and the remaining two patients died. Plasma exchange was used in 12 patients, plasmapheresis in 7 patients, rituximab in 8 patients, glucocorticoids in 18 patients, cyclophosphamide in 4 patients, ciclosporin in 1 patient, methotrexate in 1 patient, and bortezomib in 1 patient. 15 patients had a favorable prognosis, while three patients died without plasmapheresis or plasma exchange, and two patients died after PE.

TTP is a rare and fatal disease characterised by microvascular thrombosis, involving multiple organ systems. This disorder is triggered by a series of infections, malignancies, autoimmune diseases, transplantations, pregnancies and drugs [20].

For PRES, its pathophysiology is still unknown. The widely accepted hypotheses include the following: (1) the rapidly increased blood pressure exceeds the automatic regulation ability of cerebral blood flow, resulting in cerebral vasodilation and vasogenic oedema; (2) immunosuppressants damage the vascular endothelium and make plasma leak out of capillary wall, thereby causing vasogenic oedema; and (3) the damage of the blood-brain barrier caused by autoantibodies and immune complexes in patients with immune diseases is also a cause of PRES [21].

The associations between ITTP, PRES, and SS are rarely explored. In this case report, predisposing factors for TTP were not observed, such as autoimmune diseases excluding SS, malignant tumours, or infectious diseases. Thus, the reason why the patient in our case report experienced TTP and PRES was thought to be related to PSS. The ADAMTS-13 inhibitor might be an anti-ADAMTS-13 IgG associated with SS, and the appearance of PRES was probably due to endothelial dysfunction secondary to SS and TTP. A recent preclinical investigation suggested that SS may cause the failure of the precursor endothelial pool, thereby hindering vascular endothelial restoration [22]. The resulting vascular endothelial damage stimulates the release of vWF, and aggravates the microthrombi formation in TTP [23], while vWF binding to platelets further affects the regeneration and repair of the vascular endothelium, eventually leading to the occurrence of the disease.

Rituximab is a chimeric monoclonal anti-CD20 antibody that depletes B-lymphocytes. Whether given weekly or monthly, Rituximab is present at therapeutic levels in the circulation of patients for months at a time. As an IgG, rituximab distributes in both the intravascular and extravascular compartments [24], therefore, rituximab therapy could deplete B lymphocytes from peripheral blood and cerebrospinal fluid of patients [25]. In vitro studies suggested rituximab-induced signaling could contribute to death of B cell lines and synergize with cytotoxic therapy, and relevant data presented that rituximab-mediated signaling, complement dependent cytotoxicity and antibody dependent cellular cytotoxicity all contribute to rituximab's activity [24,26]. The different mechanisms of action and the interaction between them may partially explain why rituximab combined with other immunosuppressants is more effective than using some immunosuppressants alone. Although there are current reports that rituximab may cause PRES [27–29], considering the situation where the appearance of PRES and ITTP was in association with SS, we selected rituximab as a supplemental immunosuppressant. There are current reports that rituximab treatment is effective for lasting remission [30], and acute refractory or relapsing idiopathic TTP in patients with and without ADAMTS-13-inhibitory antibodies [31]. Glucocorticoids and other immunosuppressants, such as methylprednisolone, bortezomib, and cyclosporine A, are also effective in the treatment of TTP, because of to their ability to inhibit the production of autoantibodies and reduce inflammatory reactions. However, in refractory and relapsed TTP cases, the effects of additional therapy with immunosuppressive drugs (such as steroids, cyclophosphamide, or cyclosporine) has been still uncertain [31]. PE is an effective treatment for TTP because of the clearance of antibodies against ADAMTS-13 protease,

Table 1
Cases of Sjogren's syndrome associated with thrombotic thrombocytopenic purpura described in the literature.

Author, year	number, gender	Age, year	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Refractory thrombotic thrombocytopenic purpura	treatment after the diagnosis of RTTP	Outcome
Song et al., 2023	1, female	45	SS TTP PRES	yes	Anemia, thrombocytopenia, headache , consciousness alteration , schistocytes	ANA , anti–SS–A , anti- SS-B	methylprednisolone, ciclosporin, plasma exchange(PE), IVIG and rituximab	Yes	rituximab	Entirely recovered at day 95
Kasturiarachi et al., 2022 [4]	1, female	19	TTP SS	No. She had COVID-19	Anemia, thrombocytopenia, headache , consciousness alteration , schistocytes, Fever	ANA , anti-Ro/SS-A, and anti-La/SS-B	eleven sessions of plasmapheresis (PP), pulse dosed methylprednisolone for 5 days, and once weekly rituximab 8.3 mg/kg for 4 weeks	No		Recovered
Zhou et al., 2021 [5]	1, female, pregnancy, week 36	25	SS TTP	Yes	Anemia, thrombocytopenia, slight proteinuria, hypoxaemia, bilateral hydrotho rax,and heart failure	Anti–SS–A/60KD (+), anti–SS–A/52KD (++), and ANA (+)	PE; methylprednisolone 40mg/day; immunoglobulin 20g/day; rituximab(375mg/m2 qw * 2 w, 100mg/m2 qw * 2 w)	No		Recovered
Hegde et al., 2021 [6]	1, male	35	TTP PRES SS	Yes	Anemia, thrombocytopenia, confusion , fever, headache	anti-Ro/SS-A	high dose steroids , Rituximab and PP	No		Recovered
Carvalho et al., 2021 [7]	1, female	30	TTP SS, 3 months	Yes	Anemia, thrombocytopenia, consciousness alteration, renal failure, schistocytes	ANA, anti-Ro/SS-A	PP, GC, rituximab	No		Recovered
Okumura et al., 2020 [8]	1, male	47	SS TTP	Yes	Fever, anemia, thrombocytopenia, consciousness alteration, 3.6 % schistocytes	ANA, anti-Ro/SS-A	PE, GC pulse therapy, rituximab(375 mg/m2, once a week for 4 weeks)	Yes	rituximab	Entirely recovered at day 40
Sun et al., 2018 [9]	1, female	47	SS TTP, 8 years	Yes	Fever, headache, anemia, thrombocytopenia	ANA Anti-Ro/SS-A 52 kDa Anti-Ro/SS-A 60 kDa Anti-La/SS-B	PE; GC, cyclosporine, rituximab, IVIg, hydroxychloroquine, bortezomib	Yes	rituximab ineffective , add bortezomib	Recovered
Xu et al., 2017 [10]	1, male	56	Simultaneous SS and TTP	Yes	Fever, consciousness alteration, anemia, thrombocytopenia, schistocytes	ANA, anti-Ro/SS-A, and anti-La/SS-B	PE, GC, CYC	No		Recovered. Discharged on day 23
Toumeh et al., 2014 [11]	1, female	55	Simultaneous SS and TTP	Yes	Anemia, thrombocytopenia, renal impairment	ANA, anti-Ro/SS-A, and anti-La/SS-B	GC, PP, rituximab	Yes	rituximab	Recovered

(*continued on next page*)

Table 1 (*continued*)

Author, year	number, gender	Age, year	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Refractory thrombotic thrombocytopenic purpura	treatment after the diagnosis of RTTP	Outcome
Koga et al., 2013 [12]	1, female	61	SS TTP, 13 years	Yes	Anemia, thrombocytopenia, increased creatinine	ANA, anti-Ro/SS-A, and anti-La/SS-B	GC pulse therapy; GC and low molecular weight heparin (2000 U/day),PE	No		Recovered Discharged at day 65
Yamashita et al., 2012 [13]	1, female	35	Simultaneous SS and TTP	Yes	Anemia, thrombocytopenia, consciousness alteration, renal failure, schistocytes	ANA, anti-Ro/SS-A, and anti-La/SS-B	PE, GC	No		Recovered
Yamashita et al., 2012 [13]	1, female	65	Simultaneous SS and TTP	Yes	Anemia, thrombocytopenia, schistocytes	ANA, anti-Ro/SS-A, and anti-La/SS-B	PE, GC	No		Recovered
Lin et al., 2012 [14]	1, female	41	SS TTP, 3 months	Yes	Anemia, thrombocytopenia, consciousness alteration, schistocytes	ANA, anti-Ro/SS-A, and anti-La/SS-B	Methylprednisolone (40 mg, q6h), CYC，PP	Yes	cyclophosphamide	Recovered
Abe et al., 2004 [15]	1, female	75	Concomitant TTP and SS	Yes	Anemia, thrombocytopenia, macroscopic hematuria, creatinine 3.49 mg/dl, consciousness alteration	ANA, anti-Ro/SS-A, and anti-La/SS-B	GC, hemodialysis, GC pulse therapy, and double-filtration plasmapheresis for glomerulonephritis，PE	Yes	an aggravation of symptoms after PE	Died
Schattner et al., 2002 [16]	1, female	52	TTP SS, 4 months	Yes	Anemia, thrombocytopenia，schistocytes，consciousness alteration	Anti-Ro/SS-A	PE (40 ml/kg daily) for 6 consecutive days, and with aspirin and folic acid	No		Recovered after 1 relapse
Campbell et al., 1998 [17]	1, female	54	SS TTP, 3 years	Yes	Anemia, thrombocytopenia, Consciousness alteration, fever, schistocytes, mild increase creatinine, headache	ANA, anti-Ro/SS-A	High-volume PP with PE and high GC,MTX, cyclophosphamide	No		Recovered. Discharged on day 10. Relapse 33 days after treatments with GC and plasmapheresis and CYC
Noda et al., 1990 [18]	1, female	62	SS TTP	No. She had dermatomy-ositis	Anemia, thrombocytopenia, increased creatinine, consciousness alteration	ANA, anti-Ro/SS-A	prednisolone 60mg daily,PE	Yes	respiratory failure on the 10th day after the first PE	Died of respiratory failure on the 10th day
Steinberg et al., 1971 [19]	1, female	49	SS TTP; 7 years	RA and SS	Fever, thrombocytopenia, consciousness alteration, schistocytes，anemia，headache		Glucocorticoid	No PE or PP		Died

(*continued on next page*)

Table 1 (*continued*)

Author, year	number, gender	Age, year	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Refractory thrombotic thrombocytopenic purpura	treatment after the diagnosis of RTTP	Outcome
Steinberg et al., 1971 [19]	1, female	51	SS TTP; 7 years	Yes	Fever, thrombocytopenia, consciousness alteration, schistocytes , anemia , headache	RF		No PE or PP		Died
Steinberg et al., 1971 [19]	1, female	64	SS TTP; 21 years	Yes	Fever, thrombocytopenia, consciousness alteration, schistocytes , anemia , headache	ANA	40 mg of prednisone per day	No PE or PP		Died

while it is not very effective in case of secondary TTP [31]. Furthermore, owing to the need for a prolonged indwelling plasma exchange catheter in patients with refractory ITTP, the catheter-related risk of infection and immune protection should receive special attention. Additionally, patients are highly likely to develop severe infections, especially when receiving methylprednisolone, cyclosporine, and rituximab, simultaneously.

We also observed that although some patients were diagnosed with SS after TTP, clinical evidence suggested that SS might be present earlier (recalling symptoms of dryness of the eyes and mouth, and evidence of imaging features of the parotid gland), which suggested the importance of tracking medical history and related symptoms. Furthermore, this may be more difficult in patients with neurological symptoms, especially those with impaired consciousness and without severe symptoms such as eye and mouth dryness. However, further clinical observations are needed to determine whether this condition exists in all patients diagnosed with SS after TTP and how TTP causes SS.

8. Conclusions

This present study analysed the rarity of the association of SS with ITTP and PRES. This investigation suggested that most patients were female, and had PSS; and the appearance of SS before developing TTP was more common. Most patients had a favorable prognosis, who received treatment of glucocorticoids, immunosuppressants, plasmapheresis, plasma exchange, and biological agents. For SS presenting with refractory ITTP and PRES, rituximab may be of additional value.

Ethics approval and consent to participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethic committee of Qianfoshan Hospital. The written informed consent was obtained from the participants.

Consent for publication

Not applicable.

Availability of data and materials

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

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CRediT authorship contribution statement

Qicheng Song: Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zhankui Wang:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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