



CASE REPORT

# Sjögren's Syndrome Associated With Thrombotic Thrombocytopenic Purpura: A Case-Based Review

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Received: November 2, 2020 / Accepted: November 26, 2020 / Published online: December 14, 2020  
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## ABSTRACT

**Objective:** To review all published cases of the rare association between thrombotic thrombocytopenic purpura (TTP) and Sjögren's syndrome (SS). The authors report an additional case of this unique association.

**Methods:** Systematic review of the literature and a case report. The database were articles published in PubMed/MEDLINE, Web of Science, LILACS, and SciELO, registered from 1966 to August 2020. The DESH terms were "Sjögren's syndrome" and "thrombotic thrombocytopenic purpura," without language limitation.

**Results:** Most patients were female (88%), and the age varied from 30 to 75 years old. Concerning the sequence of disease appearance, SS followed by TTP was seen in seven articles, TTP and SS in three, and simultaneous appearance of both diseases in three studies. Primary SS was observed in 16 patients, and secondary SS was detected in two cases: dermatomyositis and rheumatoid arthritis. Anemia was the most common TTP manifestation, followed by thrombocytopenia, fever, consciousness alteration, renal impairment, and schistocytes' appearance on a blood smear. Treatment involved plasmapheresis, plasma exchange, rituximab, glucocorticoid, and cyclophosphamide. A good outcome was noted in most studies; few patients died.

**Conclusions:** TTP is a rare manifestation associated with SS. After the TTP diagnosis, plasmapheresis and/or plasma exchange should be immediately implemented.

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**Keywords:** Autoantibodies; Autoimmunity; Sicca syndrome; Thrombosis; Thrombotic thrombocytopenic purpura; Sjögren's syndrome

### Key Summary Points

Sjögren's syndrome (SS) associated with thrombotic thrombocytopenia purpura (TTP) is a rarity.

We performed a systematic review on all published cases of this rare association.

Most cases are female and with primary SS, and also SS appeared commonly first than TTP.

Most cases were successfully treated with glucocorticoid, plasma exchange, and plasmapheresis.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13286219>.

## INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by dryness of the eyes and mouth and involvement of diverse organs and systems. It is a common disease; it may affect 0.1–4.8% of the European population [1].

The organs commonly involved are the lungs through interstitial pneumonia, kidneys with glomerulonephritis, and renal tubular acidosis. The nervous system with peripheral neuropathies, and hematological disturbances with leucopenia, and thrombocytopenia are frequently encountered [2]. In this regard, thrombotic thrombocytopenic purpura (TTP) has been described in a few patients diagnosed with SS.

TTP is a rare, life-threatening disease with an incidence of two people per million per year, and it occurs due to severe deficiency of the von Willebrand cleaving protease, ADAMTS13 (a

disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), caused by anti-ADAMTS13 antibodies, leading to the formation of platelet-rich thrombi in the microvasculature. Clinically, it is characterized by hemolytic anemia and thrombocytopenia owing to microangiopathy anemia, consciousness alterations, fever, and renal impairment [3]. Some reports of TTP with SS are available in the literature with these conditions [4–16].

This article aims to report an additional case of a patient with TTP, subsequently diagnosed as primary SS. Furthermore, an extensive review of the literature on SS and TTP was performed.

## METHODS

### Literature Review

A systematic research of articles published in PubMed/MEDLINE, Web of Science, LILACS, and SciELO, registered from 1966 to August 2020, was performed. All the researched articles are based on the following DESH terms “Sjögren's syndrome” and “thrombotic thrombocytopenic purpura” without language limitation. Furthermore, a detailed case report on a patient with TTP subsequently diagnosed with SS is herein reported. The following parameters were screened for the published cases of SS and TTP association: demographic characteristics (gender, age), clinical features (clinical presentation of TTP, SS, and SS-related antibodies detection, the onset of symptoms and progression), therapy provided, and the response to this therapy. This article followed the PRISMA guidelines [17]. Informed consent was obtained from the patient.

### Case Report

A 30-year-old Caucasian and black mixed ethnicity female patient with a past medical history of convulsion since in her childhood has been treated until now with carbamazepine. She was admitted in April of 2014 with petechiae over her legs and dark urine, and thrombocytopenia (platelets 5000/mm<sup>3</sup>). The patient received

methylprednisolone pulse therapy 1 g daily for 3 days, and the platelets increased to 20,000/mm<sup>3</sup>. During the hospital stay, she had three absence episodes and severe hypotension and was transferred to the intensive care unit (ICU). In that place, severe hemolytic anemia (hemoglobin 5 g/dl), thrombocytopenia, renal impairment, and oscillations of conscience level were verified with schizocytes. A diagnosis of thrombotic thrombocytopenic purpura was determined, and plasmapheresis was started. She received 15 sessions of plasmapheresis, and 1 month later, rituximab was infused. After this approach, the TTP improved, and the patient recovered from this condition. Due to antinuclear antibody positivity with a titer of 1:640, a diagnosis of lupus was considered, and hydroxychloroquine 400 mg/day was prescribed. However, she did not have any evidence of skin lesions, serositis, glomerulonephritis, or polyarthritis. She has a cousin with lupus and an aunt with rheumatoid arthritis. After discharge, she went to our private clinic, and her physical examination was unremarkable. No sign of carbamazepine intoxication was found, such as gingival hypertrophy. Laboratory tests demonstrated positive antinuclear antibodies with a titer of 1:640, and a speckled pattern on indirect immunofluorescence in HEp2 cells. Anti-Ro/SS-A, anti-La/SS-B, anti-RNP, anti-Sm, anti-dsDNA, lupus anticoagulant, IgG, IgM, and IgA anticardiolipin, anti-thyroperoxidase, ANCA, anti-thyroglobulin; IgA and IgG anti-gliadin, anti-endomysium and anti-tissue transglutaminase antibodies and cryoglobulins were not detected. Complement levels were within normal range (CH50 97 U/ml, C3 150 mg/dl, and C4 30 mg/dl). Blood cell count, creatinine, and urine spot were normal. Tests for thrombophilia were all negative or within normal range: factor V Leiden, mutant prothrombin, antithrombin III, proteins C and S, and homocysteine. Serology for infectious diseases was negative: HIV 1 and 2, HTLV I and II, syphilis, cytomegalovirus, and hepatitis B and C viruses. Hemolysis test was negative at that moment, with a negative Coombs test, haptoglobin 240 mg/dl (25–190 mg/dl), normal bilirubin, and negative for schistocytes. ADAMTS 13 activity was less

than 2% (> 50%) and ADAMTS13 antigen was 0.1 (0.6–1.6). She complained of xerostomia and xerophthalmia. Salivary gland scintigraphy showed a decrease in salivary production bilaterally on submandibular and parotid glands. Schirmer test was < 5 mm in 5 min in both eyes, and Bengal rose tests were positive with a score > 5. A minor salivary gland biopsy was positive with focal lymphocytic sialadenitis and a focus score of 1 foci/4 mm. A diagnosis of primary Sjögren's syndrome was then determined. Hydroxychloroquine was kept, and ocular lubricants were added. She is currently asymptomatic; under HCQ and lubricants, routine laboratory tests are within the normal range.

## RESULTS

A total of 13 articles were found with 17 patients with SS and TTP. The analysis was performed with these 18 patients, including our case report.

Table 1 summarizes all cases of SS associated with TTP published in the literature, and our case report was added.

Regarding country of publication, the most cases came from Japan ( $n = 5$ ), followed by China ( $n = 2$ ), United States ( $n = 2$ ), Norway ( $n = 1$ ), Taiwan ( $n = 1$ ), Israel ( $n = 1$ ), Australia ( $n = 1$ ), and Brazil ( $n = 1$ ). Most patients were female 15/17 (88%), and age varied from 30 to 75 years old.

About the sequence of disease appearance, SS followed by TTP was seen in seven articles, TTP and then SS in three, and simultaneous appearance of both diseases in three studies.

Primary SS was observed in 16/18 (88.9%) patients, and secondary SS was detected in 2/18 (11.1%) cases: dermatomyositis ( $n = 1$ ) and rheumatoid arthritis ( $n = 1$ ).

Anemia was seen in 16/18 (88.9%) patients, thrombocytopenia in 15/18 (83.3%), fever in 6/18 (33.3%), consciousness alteration in 8/18 (44.4%), renal impairment in 7/18 (38.9%), and schistocytes in 7/18 (38.9%).

SS-related autoantibodies were distributed as follows: ANA in 13 articles, anti-Ro/SS-A in 12,

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

Author, year	Country	N, gender	Age, years	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Outcome
Carvalho et al. 2020 (present article)	Brazil	1, female	30	TTP SS, 3 months	Yes	Anemia, thrombocytopenia, consciousness I alteration, renal failure, schistocytes	ANA, anti-Ro/SS-A	Plasmapheresis, GC, rituximab	Recovered
Okumura et al. 2020 [4]	Japan	1, male	47	SS TTP	Yes	Fever, anemia, thrombocytopenia, consciousness alteration, 3.6% schistocytes	ANA, anti-Ro/SS-A	PE, plasmapheresis, GC pulse therapy, rituximab	Entirely recovered at day 40
Sun et al. 2018 [5]	China	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, and IVIg; hydroxychloroquine simultaneously, bortezomib	Recovered
Xu et al. 2017 [6]	China	1, male	56	Simultaneous SS and TTP		Fever, consciousness alteration, anemia, thrombocytopenia, schistocytes	ANA, anti-Ro/SS-A, and anti-La/SS-B	PE, GC, CYC	Recovered. Discharged on day 23
Jonsson et al. 2015 [7]	Norway	1, female	35	TTP SS,	Yes	Fever, thrombocytopenia, anemia, 5% schistocytes, mild increase in creatinine	ANA, anti-Ro/SS-A	Freshly frozen plasma transfusion, and 5 daily PE	Normal after 13 weeks
Toumeh et al. 2014 [8]	United States	1, female	55	Simultaneous SS and TTP	Yes	Anemia, thrombocytopenia, renal impairment	ANA, anti-Ro/SS-A, and anti-La/SS-B	GC, plasmapheresis, rituximab	Recovered

**Table 1** continued

Author, year	Country	N, gender	Age, years	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Outcome
Koga et al. 2013 [9]	Japan	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)	Recovered Discharged at day 65
Yamashita et al. 2012 [10]	Japan	2, female	35, 65	Simultaneous SS and TTP	Yes	Anemia, thrombocytopenia, consciousness I alteration	ANA, anti-Ro/SS-A, and anti-La/SS-B	PE 3 times PE, GC	Recovered
Lin et al. 2012 [11]	Taiwan	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	Recovered
Abe et al. 2004 [12]	Japan	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	Died
Schattner et al. 2002 [13]	Israel	1, female	52	TTP SS, 4 months	Yes	Anemia, thrombocytopenia	Anti-Ro/SS-A	PE (40 ml/kg daily) for 6 consecutive days, and with aspirin and folic acid	Recovered after 1 relapse
Campbell et al. 1998 [14]	Australia	1, female	54	SS TTP, 3 years	Yes	Consciousness alteration, fever, vomiting, and diarrhea. Schistocytes, mild increase creatinine	ANA, anti-Ro/SS-A	High-volume plasmapheresis with PE and high GC	Recovered. Discharged on day 10. Relapse 33 days after treated with GC and plasmapheresis and CYC

Table 1 continued

Author, year	Country	N, gender	Age, years	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Outcome
Noda et al. 1990 [15]	Japan	1, female	62	SS TTP	No. She had dermatomyositis	Anemia, thrombocytopenia, increased creatinine	ANA	PE	Died of respiratory failure on the 10th day
Steinberg et al. 1971 [16]	United States	3, female	49, 51, 64	SS TTP; 7, 7 and 21 years	Case 1; RA and SS Case 2; primary SS Case 3: Primary SS	Fever, thrombocytopenia, consciousness alteration, schistocytes	ANA ( <i>n</i> = 1), RF ( <i>n</i> = 1)	Glucocorticoid	All died within 2 weeks

ANA antinuclear antibodies, CYC cyclophosphamide, GC glucocorticoid, IVIg intravenous immunoglobulin, PE plasma exchange, RF rheumatoid factor, SS Sjögren's syndrome, TTP thrombotic thrombocytopenic purpura

anti-La/SS-B in seven, and rheumatoid factor in one.

Treatment involved plasmapheresis in six studies, plasma exchange in eight articles, rituximab in four, glucocorticoid in 11, and cyclophosphamide in two.

A good outcome was noted in 11 articles, and patients died in three articles with four patients. In one study (1971), two patients died; neither plasmapheresis nor plasma exchange was used.

## DISCUSSION

This article is an additional report of a patient who suffered from TTP and subsequently had a SS diagnosis. We followed the PRISMA guidelines [17], which is strongly recommended in a systematic review analysis.

Most patients had SS before the TTP development. This suggests that SS may have a pathophysiological role in initiating the microangiopathy. It is known that SS may present with vasculitis and the presence of several autoantibodies. SS has classical autoantibodies like antinuclear antibodies, anti-Ro/SS-A, and anti-La/Ss-b, a new article describes 19 novel autoantibodies in SS [18]. It will not be a surprise if investigated anti-ADAMTS13 antibodies might be found in SS without TTP.

The TTP initial diagnosis should be based on the history, physical examination, routine laboratory tests, and schistocytes definitive presence on the peripheral blood smear. Patients generally present with signs and symptoms and have laboratory abnormalities that reflect the underlying microvascular thrombi. A low baseline ADAMTS13 activity of 10% or less, as observed in our patient, with or without an anti-ADAMTS13 autoantibody, in the association with thrombocytopenia microangiopathic hemolytic anemia are highly suggestive of TTP. However, the classic “pentad” of clinical features is very typical for TTP, and it may appear in only 5% of patients. Therefore, after the TTP’s clinical suspicion, rapid treatment is mandatory, even without ADAMTS13 levels detection. The treatment of TTP involves plasma exchange and glucocorticoids. When

the disease is refractory to these therapeutical agents, the physician may increase plasma exchange twice daily, add rituximab, methylprednisolone pulse therapy, cyclosporine, and cyclophosphamide vincristine, and splenectomy [19].

TTP’s risk factors are genetics that includes the black race, probably due to the lower frequency of the protective allele for TTP, HLA-DRB1\*04. Interestingly, black people with TTP may better survive than white patients, despite comparable disease severity [20]. Our patient was Caucasian and black mixed ethnicity and it might explain her risk for TTP and good survival. In lupus patients, lymphopenia, high SLEDAI score 3 months before hospitalization, low hemoglobin levels, low levels of indirect bilirubin, and less severe thrombocytopenia were all independent risk factors in these patients for TTP development [21]. Moreover, in another study, the multivariate analysis showed that infection was the only independent risk factor for mortality in lupus patients with TTP [22]. In a different non-autoimmune condition, post-bone marrow transplant, patients who developed TTP were three times older and more twice as likely to be female compared to those cases who had not evolved to TTP [23]. Another study found that the black race and blood group O are independent risk factors for TTP [24]. Relying on these previous studies in other diseases, which evolved to TTP, female sex, old age, disease activity, blood group O, and infections, seem to be the central risk factors for TTP. These findings agree with the present review since most SS patients associated with TTP were female, and 10/17 were more than 50 years old. However, the articles do not describe an infection or SS disease activity.

## CONCLUSIONS

In conclusion, this systematic review analyzed the rarity of SS associated with TTP, and verified that most cases are female and with primary SS, and also SS appeared more commonly before TTP development. Most cases were successfully treated with glucocorticoids, plasma exchange, and plasmapheresis.



## ACKNOWLEDGEMENTS

The authors would like to thank Sergio Ribeiro for the English revision of the manuscript.

**Funding.** No funding or sponsorship was received for this study or publication of this article.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosures.** Jozélio F. Carvalho is on the editorial board for *Rheumatology and Therapy* but has nothing else to disclose. Yehuda Shoenfeld has nothing to disclose.

**Compliance with Ethics Guidelines.** The authors declare that the World Medical Association Declaration of Helsinki were followed. Informed consent was obtained from the patient for publication of this study.

**Data Availability.** Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study. We thank the patient, participant of this study.

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