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Case Report **Nephrology Hemodialysis**

Thrombotic Thrombocytopenic Purpura Complicating Secondary Sjögren's Syndrome: A Rare and Serious Association from Africa

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Abstract

Thrombotic Thrombocytopenic Purpura is a potentially fatal disease that can be life-threatening. The association with Sjogren's syndrome is rare entity that deserves special attention. To this end, we report the case of a Thrombotic thrombocytopenic purpura complicating secondary Sjögren's syndrome. This is a 49-year-old patient with a history of pure nephrotic syndrome with minimal glomerular lesions (LGM), who developed Sjögren's syndrome two years later. The diagnosis of Sjögren's syndrome was retained with an etiological investigation suggesting SS secondary to SLE systemic lupus erythematosus. Six months after the diagnosis of secondary SS, the patient was admitted with headache, ecchymotic and petechial lesions on the upper limbs. The laboratory analysis revealed severe thrombocytopenia, haemolytic anemia with a schizocyte count at 6% supporting the diagnosis of thrombotic microangiopathy. The ADAMTS 13 activity assay was less than 5% and the anti-ADAMTS 13 antibody test was positive, attesting thus, the diagnosis of acquired TTP complicating SS secondary to SLE. The patient received an emergency blood transfusion of fresh frozen plasma combined with corticosteroid therapy and mycophenolate mofetil. The clinico-biological outcome, at 6 month and 1 year, was favorable with complete remission. To the best of our knowledge, this is the first case report of TTP complicating Sjögren's syndrome in Africa. It highlights the rarity of association between autoimmune disease particulary Sjögren's syndrome and TTP.

Keywords: Thrombotic Thrombocytopenic Purpura, Sjogren's syndrome, LGM, diagnosis.

INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by xerophthalmia and xerostomia that can also manifest itself by respiratory, renal, neurological and haematological involvement. In this regard, thrombotic thrombocytopenic purpura (TTP) has been described in a few patients diagnosed with SS.

In this article, we will report the observation of a patient who was diagnosed with thrombotic thrombocytopenic purpura complicating secondary Sjögren's syndrome, with a literature review on the associations of TTP and SS.

OBSERVATION

We report the case of a 49-year-old patient with a history of pure nephrotic syndrome with minimal glomerular lesions (LGM) who presented with a relapse treated so far with cyclophosphamide at a dose of 2 mg/kg/day for 2 months, bringing the cumulative dose to 13g with good clinico-biological outcome. Two years later, the patient developed dry oculo-oral syndrome with diffuse arthralgia and psoriasiform skin lesions. Immunolaboratory testing showed positive anti-SSA "52KD" antibodies, Schirmer's test was < 5 mm in 5 min in both eyes, and salivary gland biopsy was positive for grade three lymphocytic sialadenitis according to the Chisholm and Mason classification.

The diagnosis of Sjögren's syndrome was retained with an etiological investigation suggesting SS secondary to SLE systemic lupus erythematosus (positive antinuclear antibodies, skin symptoms, joint involvement and lymphopenia) according to ACR

classification criteria; justifiying the prescription of hydroxychloroquine at a dose of 400mg per day and symptomatic treatment with artificial tears and mouth gel.

Six months after the diagnosis of secondary SS, the patient was admitted with diffuse petechiae and headache. Clinical examination found a conscious patient, stable hemodynamically and respiratory. He was subfebrile at 38°C, with ecchymotic and petechial lesions on the upper limbs and inactive urinary sediment. The laboratory analysis revealed severe thrombocytopenia at 20000 platelets, haemolytic anemia with haemoglobin at 5g/dl and a schizocyte count at 6% supporting the diagnosis of thrombotic microangiopathy. The ADAMTS 13 activity assay was less than 5% and the anti-ADAMTS 13 antibody test was positive, attesting thus, the diagnosis of acquired TTP complicating SS secondary to SLE.

The patient received an emergency blood transfusion of fresh frozen plasma combined with seven daily plasma exchanges, daily pulses of methylprednisolone 1g for 3 days relayed by oral corticosteroid therapy and mycophenolate mofetil 2g/day gradually reached.

The clinico-biological outcome, at 6 month and1 year, was favorable with complete remission.

Table 1: The epidemiological characteristics, therapeutic methods and evolution of SS-associated TTP cases in the literature

Continent	Country	Author/ year	Sex/Age	Disease sequence	Primary SS (pSS)/ Secondary SS (sSS)	Treatment	Outcome
Asia (10 cases)	**China**	Zhou *et al.*, 2021 [4]	Female 25 years	TTP=SS	pSS	Rituximab PE	Recovered
		Sun *et al.*, 2018 [5]	Female 47 years	SS/TTP (8 years)	pSS	Rituximab PE GC	Recovered
		Xu *et al.*, 2017 [6]	Male 56 years	TTP=SS		CYP GC PE	Recovered
	Japan	Okumura *et al.*, 2020 [7]	Male 47 years	SS/TTP	pSS	Rituximab PE GC	Recovered
		Koga *et al.*, 2013 [8]	Female 61 years	SS/TTP (13 years)	pSS	PE GC	Recovered
		Yamashita *et al.*, 2012 [9]	2 Females 35/65 years	SS=TTP	pSS	PE GC	Recovered
		Abe *et al.*, 2004 [10]	Female 75 years	SS=TTP	pSS	PE GC	Died
		Noda *et al.*, 1990 [11]	Female 62 years	SS/TTP	sSS Dermato-myosis	PE GC	Died
	Taiwan	Lin *et al.*, 2012 [12]	Female 41 years	SS/TTP (3 months)	pSS	GC CYP PE	
America (5 cases)	**Brazil**	Carvalho *et al.*, 2020 [13]	Female 30 years	TTP/SS (3 months)	pSS	Rituximab PE GC	Recovered
	US	Toumeh *et al.*, 2014 [14]	Female 55 years	SS=TTP	pSS	Rituximab GC PE	Recovered
		Steinberg *et al.*, 1971[15]	3 Females 49/51/64 years	SS/TTP	sSS (RA) 2 pSS		Died
Europe (2 cases)	**Norway**	Jonsson *et al.*, 2015[16]	Female 35 years	TTP/SS	pSS	FFP PE	Recovered
	Israel	Shattner *et al.*, 2002[17]	Female 52 years	TTP/SS (4 months)	pSS	PE	Recovered and relapsed 3 months later
Australia (1 case)	**Austra-lia**	Campbell *et al.*, 1998 [18]	Female 54 years	SS/TTp (3 months)	pSS	PP PE GC	Recovered and relapsed 1 month later
Africa (1 case)	**Moro-cco**	Azizi *et al.*, 2023	Male 45 years	SS/TTP (6 months)	sSS LED	GC MMF	Recovered one year later

DISCUSSION

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by oculo-buccal dry syndrom and multiple organ damage. It is a widespread disease that affect 0.1 to 4.8% of the European population [1]. Commonly affected organs are lungs through interstitial pneumonia, kidneys by glomerulonephritis and renal tubular acidosis. Nervous system disorders and haematological damage such as leucopenia and thrombocytopenia are also described [2]. In this context, thrombotic thrombocytopenic purpura (TTP) has been reported in a few patients diagnosed with SS.

TTP is a rare and potentially fatal disease with an incidence of two people per million per year. It is due to a severe deficiency of the cleavage protease of Von Willebrand factor ADAMTS13, generated by anti-ADAMTS13 antibodies, leading to the formation of platelet-rich thrombus in the microcirculation. TTP is characterized by mechanical hemolytic anemia, thrombocytopenia, impaired consciousness, fever, and renal failure [3].

Low initial activity ADAMTS13 at 10% or less, as in our patient, with or without anti-ADAMTS13 autoantibodies, in association with hemolytic anemia and thrombocytopenia is highly evoking TTP. However, the classic clinical "pentad" of TTP may occur in only 5% of patients. Therefore, as soon as TTP is clinically suspected, prompt plasma exchange and glucocorticoid treatment is imperative, even without detection of ADAMTS13 levels [2].

Table 1 presents the epidemiological characteristics, therapeutic methods and evolution of SS-associated TTP cases in the literature. Indeed, the distribution of TTP is cosmopolitan; most cases have been reported in Asia, particularly Japan (5 cases) and China (3 cases) [4-11]. The majority of patients are women with ages ranging from 25 to 75 years. Regarding the sequence of disease onset, most patients had SS prior to TTP development [4-18]. This suggests that SS may have a pathophysiological role in the initiation of microangiopathy [19]. Nevertheless, TTP can happen concurrently with the diagnosis of SS [4, 6, 9, 10, 14] or precede it in rare cases [13, 16, 17]. Furthermore, the SS associated with TTP is often primary [4-10,12-18]. In rare cases, it is secondary to dermatomyositis [11] and rheumatoid arthritis [15]. In our patient, TTP occurred 6 months after the diagnosis of SS and it was secondary to systemic lupus.

The most SS-related autoantibodies frequently found are antinuclear antibodies, followed by anti-Ro/SS-A and then anti-La/SS-B. In our patient, the antibodies found were mainly antinuclear and anti-Ro/SS-A. Anemia was the most common manifestation of TTP, followed by thrombocytopenia, fever, altered consciousness, renal failure and the appearance of schizocytes on the blood smear [4-18]. Our patient presented clinically with fever, headache and diffuse petechial lesions with biologically, anemia and thrombocytopenia associated with presence of schizocytes on blood smear indicating the mechanical nature of the anemia. However, he had no kidney damage even he were treated for idiopathic nephrotic syndrome with minimal glomerular lesions in the past.

Treatment is based, as soon as possible, on initiation of plasma exchanges with transfusion of fresh frozen plasma, thus eliminating anti-ADAMTS 13 autoantibodies and restoring the circulating level of ADAMTS factor 13. In addition, the treatment uses also immunosuppressive therapy so as to stop production of anti-ADAMTS13 anti bodies. In all published cases, Treatment involved plasma exchange [4,18], rituximab in 5 studies [4, 5, 7, 13, 14], glucocorticoid in 12 studies [5-14, 18], and cyclophosphamide in two studies [6, 12]. In our patient, both fresh frozen plasma and plasma exchanges were used. The immunosuppressive therapy consisted on daily pulses of methylprednisolone relayed by oral corticosteroid therapy and mycophenolate mofetil. Cyclophosphamid was avoided since our patient has reached the allowable cumulative dose when treating his renal disease. Rituximab was not considered because of its high cost.

A good result was seen in our patient and in 13 studies, on the other hand death was deplored in three other reviews. In one study conducted by steinberg and his team, two patients died; even if plasmapheresis or plasma exchange were used.

This article is an additional report from a patient with SS, who was later diagnosed as TTP. Most patients had SS prior to the development of TTP. This suggests that SS may have a pathophysiological role in the initiation of microangiopathy. It is known that SS can be accompanied by vasculitis and the presence of several autoantibodies. The classic autoantibodies in SS are antinuclear, anti-Ro/SS-A, and anti-La/SS-B antibodies, but recently new paper describes 19 new autoantibodies in SS [19].

In patients with lupus, female gender, old age, disease activity, blood type O, and infections, appear to be the main risk factors for TTP. These results agree with this review since most patients with TTP-associated SS were female and over 50 years old. However, the only risk factor in our patient was age Additionnaly, he did not show any clinical or laboratory signs of infection and his autoimmune disease was inactive.

CONCLUSION

In conclusion, SS-TTP is a rare combination and life-threatening disease. Most cases of TTP are associated with primary SS and occured often before TTP development. It is a therapeutic emergency that requires an early start of plasma exchange combined

with an efficient immunosuppressive therapy. Future studies will better characterize the natural history of SS-PTT.

REFERENCES

1. Both, T., Dalm, V. A., van Hagen, P. M., & van Daele, P. L. (2017). Reviewing primary Sjögren's syndrome: beyond the dryness-From pathophysiology to diagnosis and treatment. *International journal of medical sciences*, *14*(3), 191-200.
2. Renard, R. I. (2005). Le syndrome de Sjogren. *Lancette*, *366*(9482), 321–331.
3. Chiasakul, T., & Cuker, A. (2018). Diagnostic clinique et de laboratoire du PTT : une approche intégrée. *Programme Hematol Am Soc Hematol Educ*, *2018*(1), 530–538.
4. Zhou, L., Zhu, Y., Jiang, M., Su, J., Liu, X., Jiang, Y., ... & Liu, H. (2021). Pregnancy-associated thrombotic thrombocytopenic purpura complicated by Sjögren's syndrome and non-neutralising antibodies to ADAMTS13: a case report. *BMC Pregnancy and Childbirth*, *21*(1), 1-6.
5. Sun, R., Gu, W., Ma, Y., Wang, J., & Wu, M. (2018). Relapsed/refractory acquired thrombotic thrombocytopenic purpura in a patient with Sjögren syndrome: Case report and review of the literature. *Medicine*, *97*(43), e12989.
6. Xu, X., Zhu, T., Wu, D., & Zhang, L. (2018). Sjögren's syndrome initially presented as thrombotic thrombocytopenic purpura in a male patient: a case report and literature review. *Clinical Rheumatology*, *37*, 1421-1426.
7. Okumura, T., Hashimoto, K., Aomura, D., Kurasawa, Y., Hara, Y., Fujii, K., ... & Kamijo, Y. (2020). Thrombotic thrombocytopenic purpura treated with rituximab associated with primary Sjögren's syndrome and primary hypothyroidism. *Internal Medicine*, *59*(5), 715-719.
8. Koga, T., Yamasaki, S., Nakamura, H., Kawakami, A., Furusu, A., Taguchi, T., & Eguchi, K. (2013). Renal thrombotic microangiopathies/thrombotic thrombocytopenic purpura in a patient with primary Sjögren's syndrome complicated with IgM monoclonal gammopathy of undetermined significance. *Rheumatology international*, *33*, 227-230.
9. Yamashita, H., Takahashi, Y., Kaneko, H., Kano, T., & Mimori, A. (2013). Thrombotic thrombocytopenic purpura with an autoantibody to ADAMTS13 complicating Sjögren's syndrome: two cases and a literature review. *Modern rheumatology*, *23*(2), 365-373.
10. Abe, H., Tsuboi, N., Yukawa, S., Tsuji, S., Hayashi, H., Yukawa, N., ... & Hayashi, T. (2004). Thrombotic thrombocytopenic purpura complicating Sjögren's syndrome with crescentic glomerulonephritis and membranous nephritis. *Modern rheumatology*, *14*, 174-178.
11. Noda, M., Kitagawa, M., Tomoda, F., & Iida, H. (1990). Thrombotic thrombocytopenic purpura as a complicating factor in a case of polymyositis and Sjogren's syndrome. *American journal of clinical pathology*, *94*(2), 217-221.
12. Lin, T. Y., Chang, C. C., Chang, C. C., Yuan, J. Y., & Chen, H. H. (2012). Cyclophosphamide-rescued plasmapheresis-unresponsive secondary thrombotic thrombocytopenic purpura caused by Sjögren's syndrome. *Archives of Medical Science*, *8*(5), 934-938.
13. Carvalho, J. F., & Shoenfeld, Y. (2021). Sjögren's Syndrome Associated With Thrombotic Thrombocytopenic Purpura: A Case-Based Review. *Rheumatology and Therapy*, *8*, 621-629.
14. Toumeh, A., Josh, N., Narwal, R., & Assaly, R. (2014). Refractory thrombotic thrombocytopenic purpura associated with primary Sjogren syndrome treated with rituximab: a case report. *American journal of therapeutics*, *21*(2), e56-e60.
15. Steinberg, A. D., Green, W. T., & Talal, N. (1971). Thrombotic thrombocytopenic purpura complicating Sjögren's syndrome. *Jama*, *215*(5), 757-761.
16. Jonsson, M. K., Hammenfors, D., Oppegaard, O., Bruserud, Ø., & Kittang, A. O. (2015). A 35-year-old woman with influenza A-associated thrombotic thrombocytopenic purpura. *Blood Coagulation & Fibrinolysis*, *26*(4), 469-472.
17. Schattner, A., Friedman, J., & Klepfish, A. (2002). Thrombotic Thrombocytopenic Purpura as an Initial Presentation of Primary Sjo¨ gren's Syndrome. *Clinical rheumatology*, *21*(1), 57-59.
18. Campbell, G. N. S., & Gallo, J. H. (1998). Relapsing thrombotic thrombocytopenic purpura (TTP) in Sjogren's syndrome. *Australian and New Zealand journal of medicine*, *28*(2), 214-214.
19. Martín-Nares, E., & Hernández-Molina, G. (2019). Novel autoantibodies in Sjögren's syndrome: a comprehensive review. *Autoimmunity reviews*, *18*(2), 192-198. doi: 10.1016/j.autrev.2018.09.003.
20. Merayo-Chalico, J., Demichelis-Gómez, R., Rajme-López, S., Aparicio-Vera, L., Barrera-Vargas, A., Alcocer-Varela, J., & Gómez-Martín, D. (2014). Risk factors and clinical profile of thrombotic thrombocytopenic purpura in systemic lupus erythematosus patients. Is this a distinctive clinical entity in the thrombotic microangiopathy spectrum?: a case control study. *Thrombosis Research*, *134*(5), 1020-1027.