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Thrombotic Microangiopathy Associated to Sjogren's Syndrome: Case Report and Literature Review

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ABSTRACT

Introduction: Sjogren's syndrome (SS) is an autoimmune disease characterized by ocular and oral dryness and a variety of other systemic manifestations. Thrombotic Microangiopathy (TMA) is rarely associated with SS. We report a case that illustrates this association in a female patient, who also presents autoimmune hypophysitis.

Observation: A 65-year-old patient was referred for investigation of an axonal sensorimotor neuropathy that has been evolving for 5 months. Possible infectious and neoplastic causes were ruled out by examination, laboratory tests and imaging. The patient reported ocular and oral dryness. Minor salivary gland biopsy highlighted the presence of focal lymphocytic sialadenitis with a focus score of 1 foci/4 mm^2. Schirmer's test was inferior to 5 mm/5 min in both eyes. Laboratory investigations revealed anterior pituitary failure including secondary adrenal insufficiency, central hypothyroidism and hypogonadotropic hypogonadism. Magnetic resonance imaging of the hypothalamo-pituitary region demonstrated signs of autoimmune hypophysitis. During hospitalization, the patient developed anemia and thrombocytopenia with schizocytes count at 4%. The diagnosis of TMA associated to SS, without renal failure was made. The patient was commenced on intravenous immunoglobulin, corticosteroids, azathioprine and pregabalin. An improvement was noticed in her neuropathic pain, anemia and thrombocytopenia, schizocytes count was reduced progressively.

Conclusion: Previous systematic reviews highlighted the rarity of SS associated with TMA. Our case also illustrates two manifestations of SS: Axonal neuropathy and autoimmune hypophysitis.

Keywords: Sjogren's syndrome; Thrombotic microangiopathy; Axonal neuropathy; Anterior pituitary failure

INTRODUCTION

Thrombotic Microangiopathies (TMA) encompass a spectrum of rare but potentially lethal disorders characterized by endothelial damage. While primary forms such as thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) are well-recognized entities, secondary TMAs pose diagnostic challenges, particularly when associated with autoimmune diseases. These disorders manifest through the formation of microthrombi within small blood vessels, leading to organ damage and systemic complications. Despite their rarity, their severity demands prompt recognition and intervention.

However, within the realm of TMAs, lies a subset of secondary forms, which present a distinct diagnostic challenge, particularly when intertwined with autoimmune disorders. The complexity escalates as these secondary TMAs often exhibit overlapping clinical features with primary TMAs, making accurate diagnosis and management a formidable task for clinicians.

Autoimmune diseases, such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), and Antiphospholipid

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Syndrome (APS), can precipitate secondary TMAs through various pathogenic mechanisms involving immune dysregulation and endothelial dysfunction. These disorders not only heighten the risk of thrombotic complications but also obscure the diagnostic landscape by masquerading as primary TMAs.

Furthermore, the management of secondary TMAs necessitates a multifaceted approach, addressing both the underlying autoimmune condition and the associated thrombotic microangiopathy. Treatment strategies often involve immunosuppressive agents to mitigate autoimmune-mediated endothelial injury, alongside plasma exchange or immunomodulatory therapies targeting the thrombotic cascade.

In essence, the diagnosis and management of secondary TMAs remain intricate endeavors, demanding heightened clinical suspicion, diligent evaluation, and tailored therapeutic interventions to navigate the intricate interplay between autoimmune diseases and thrombotic microangiopathies.

CASE REPRESENTATION

A 65-year-old patient was referred for investigation of an axonal sensorimotor neuropathy that has been evolving for 5 months. Possible infectious and neoplastic causes were ruled out by examination, laboratory tests and imaging. The patient reported ocular and oral dryness. Minor salivary gland biopsy highlighted the presence of focal lymphocytic sialadenitis with a focus score of 1 foci/4 mm^2. Schirmer's test was inferior to 5 mm/5 min in both eyes. Laboratory investigations revealed anterior pituitary failure including secondary adrenal insufficiency, central hypothyroidism and hypogonadotropic hypogonadism. Magnetic resonance imaging of the hypothalamo-pituitary region demonstrated signs of autoimmune hypophysitis. During hospitalization, the patient developed anemia and thrombocytopenia with schizocytes count at 4%. The diagnosis of TMA associated to SS, without renal failure was made. The patient was commenced on intravenous immunoglobulin, corticosteroids, azathioprine and pregabalin. An improvement was noticed in her neuropathic pain, anemia and thrombocytopenia. Schizocytes count was reduced progressively.

RESULTS AND DISCUSSION

Thrombotic Microangiopathies (TMA) are rare, yet life-threatening hematologic and multisystemic conditions that are initiated by endothelial damage or dysfunction. Comprehensive history, examination and laboratory tests are crucial. The clinical manifestation of TMA can vary and be nonspecific. They include thrombocytopenia, Microangiopathic Hemolytic Anemia (MAHA), and microthrombi leading to ischemic tissue injury.

Thrombocytopenia results from platelet activation and consumption. MAHA is the hallmark of TMA. It is characterized by the fragmentation of red blood cells in the microvasculature, leading to the presence of schistocytes in peripheral blood films. Elevated lactate dehydrogenase (LDH) levels occur due to tissue ischemia and cell lysis. Reduced plasma haptoglobin serves as an indicator of hemolysis, Coombs test is typically negative [1]. Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) represent primary forms of TMA. They occur spontaneously with no associated underlying cause [2-4].

Secondary forms mainly occur in the context of pregnancy, malignant hypertension, autoimmune disease, malignancy, bone marrow transplantation or use of specific medications [2,5]. A comprehensive diagnostic evaluation is necessary to identify secondary causes, appropriate treatment of the underlying condition is necessary.

TMA secondary to autoimmune diseases were reported in many studies [6-8]. The autoimmune diseases more commonly associated with TMA are systemic lupus erythematosus, antiphospholipid syndrome and scleroderma [6,8,9]. The association of Sjogren Syndrome (SS) and TMA is uncommon. As much as we know, 29 cases have been reported to date, as described in **Table 1**. Most of the patients presented with Anemia with Schistocytes and Thrombocytopenia like our patient. Treatment was mainly based on glucocorticoids, Rituximab, intravenous immunoglobulin and plasma exchange. Our patient was commenced on intravenous immunoglobulin, corticosteroids and azathioprine. The majority of patients recovered like our patient. In our case, the patient received a regimen consisting of IVIG, corticosteroids, and azathioprine.

The therapeutic approach is largely guided by the underlying autoimmune condition and the severity of TMA manifestations. While most patients, including ours, exhibit a favorable response to treatment, the management strategy may vary. For instance, Rituximab, a monoclonal antibody targeting CD20-positive B lymphocytes, has shown efficacy in cases resistant to conventional therapy. Additionally, IVIG therapy has been proposed for its immunomodulatory effects and potential to stabilize endothelial function.

It's worth noting that the prognosis of TMA associated with autoimmune diseases hinges on several factors, including the promptness of diagnosis, the extent of organ involvement, and the efficacy of treatment. Close monitoring for disease activity and complications is paramount in ensuring optimal outcomes. Moreover, ongoing research endeavors are essential for elucidating the intricate pathophysiological mechanisms underlying this association and refining treatment strategies to improve patient outcomes.

Learning Points

- TMA secondary to autoimmune diseases like SS is uncommon but reported. Thorough diagnostic assessments and tailored therapeutic interventions are essential for managing these cases effectively.
- Despite the severity of the condition, many patients, including those with SS-associated TMA, have shown recovery with appropriate treatment.

Table1: Reported cases of TMA associated to Sjogren's syndrome

Author, year	Country	N, gender	Age, years	Disease sequence, the time between diseases	Primary SS	TTP symptoms	SS-related autoantibodies	Treatment	Outcome
Our patient	Tunisia	1, female	56	Simultaneous SS and TMA	Yes	Hemolytic anemia, schistocytes, thrombocytopeni, fever	Anti-Ro	Oral GC IVIg	Recovered
Kasturiarachi BM, et al. 2022 [10]	United states	1, female	19	Simultaneous SS and TTP	Yes	Hemolytic anemia, schistocytes, thrombocytopeni, fever, and encephalopathy	ANA, anti-SSA, anti-SSB	11 sessions of PE Pulse dosed methylprednisolone for 5 days Once weekly Rituximab 8.3 mg/kg for 4 weeks	Recovere/Discharged
Nihal Martis, et al. [6]	France	7	-	-	Yes	-	-	-	-
Rahul Hegde et al. 2021 [11]	United states	1, male	35	Simultaneous SS and TTP	Yes	Hemolytic anemia, thrombocytopenia PRES	Anti-SSA	PE Weekly Rituximab therapy for 4 doses Oral GC	Recovere/Discharged
Devon D. Miller, et al. 2021 [12]	Caucasian	1, male	72	SS, TTP	Yes	Hemolytic anemia, schistocytes, severe thrombocytopeni, acute kidney injury	ANA, anti-SSA, RF	PE daily x 14, prednisone (1 mg/kg; 110 mg)	Recovered
Santamaria, et al. 2020 [13]	Colombia	1, female	26	SS, TMA	Yes	Petechiae in lower limbs, gingivorrhagia, menorrhagia and jaundice	ANA, antiRo	Rituximab (375 mg/m2; 800 mg infusion) once a week × 4	Discharged
								Methylprednisolone 500 mg/day, 3 days) PE Cyc (750 mg)	Recovery of hemoglobin and platelet levels; however, the patient died due to a complication of the PE catheter removal procedure.
Carvalho, et al. 2020 [14]	Brazil	1, female	30	TTP SS, 3 months	Yes	Anemia, thrombocytopeni, consciousness l alteration, renal failure, schistocytes	ANA, anti-Ro/SSA	PE, GC, rituximab	Recovered
Okumura, et al. 2020 [15]	Japan	1, male	47	SS TTP	Yes	Fever, anemia, thrombocytopeni, consciousness alteration, 3.6% schistocytes	ANA, anti-Ro/SSA	PE, GC pulse therapy, rituximab	Entirely recovered at day 40
Sun, et al. 2018 [16]	China	1, female	47	SS TTP, 8 years	Yes	Fever, headache, anemia, thrombocytopenia	ANA	PE; GC, cyclosporine, Rituximab, and IVIg; hydroxychloroquine simultaneously, bortezomib	Recovered
							Anti-Ro/SSA 52 kDa		
							Anti-Ro/SSA 60 kDa		
							Anti-La/SSB		

Xu, et al. 2017 [17]	China	1, male	56	Simultaneous SS and TTP	-	Fever, consciousness alteration, anemia, thrombocytopenia, schistocytes	ANA, anti-Ro/SSA, and anti-La/SSB	PE, GC, CYC	Recovered. Discharged on day 23
Jonsson, et al. 2015 [18]	Norway	1, female	35	TTP SS,	Yes	Fever, thrombocytopeni, anemia, 5% schistocytes, mild increase in creatinine	ANA, anti-Ro/SSA	Freshly frozen plasma transfusion, and 5 daily PE	Normal after 13 weeks
Mei-Hua Cheng, et al. 2014 [9]	China	1, female	56	SS TTP	Yes	Anemia, schistocytes, thrombocytopenia	Anti-Ro	PE and a red-blood-cell transfusion for three consecutive days	Recovered, discharged
								TMA recurred two weeks later: PE Prednisolone 1 mg/kg/day Cyc	Recovered
Toumeh, et al. 2014 [19]	United States	1, female	55	Simultaneous SS and TTP	Yes	Anemia, thrombocytopenia, renal impairment	ANA, anti-Ro/SSA, and anti-La/SSB	GC, PE, rituximab	Recovered
Koga, et al. 2013 [20]	Japan	1, female	61	SS TTP, 13 years	Yes	Anemia, thrombocytopeni, increased creatinine	ANA, anti-Ro/SSA, and anti-La/SSB	GC pulse therapy; GC and low molecular weight heparin (2000 U/day)	Recovered
								PE 3 times	Discharged at day 65
Yamashita, et al. 2012 [21]	Japan	2, female	35, 65	Simultaneous SS and TTP	Yes	Anemia, thrombocytopeni, consciousness l alteration	ANA, anti-Ro/SSA, and anti-La/SSB	PE, GC	Recovered
Lin, et al. 2012 [22]	Taiwan	1, female	41	SS TTP, 3 months	Yes	Anemia, thrombocytopeni, consciousness alteration, schistocytes	ANA, anti-Ro/SSA, and anti-La/SSB	Methylprednisolone (40 mg, q6h), CYC	-
Abe, et al. 2004 [23]	Japan	1, female	75	Concomitant TTP and SS	Yes	Anemia, thrombocytopeni, macroscopic hematuria, creatinine 3.49 mg/dl, consciousness alteration	ANA, anti-Ro/SSA, and anti-La/SSB	GC, hemodialysis, GC pulse therapy, and double-filtration PE for glomerulonephritis	Died
Schattner, et al. 2002 [24]	Israel	1, female	52	TTP SS, 4 months	Yes	Anemia, thrombocytopenia	Anti-Ro/SSA	PE (40 ml/kg daily) for 6 consecutive days, and with aspirin and folic acid	Recovered after 1 relapse
Campbell, et al. 1998 [25]	Australia	1, female	54	SS TTP, 3 years	Yes Hypothyroidism	Consciousness alteration, fever, vomiting, and diarrhea. Schistocytes, mild increase creatinine	ANA, anti-Ro/SSA	High-volume plasmapheresis with PE and high GC	Recovered. Discharged on day 10. Relapse 33 days after treated with GC and plasmapheresis and CYC
Noda, et al. 1990 [26]	Japan	1, female	62	SS TTP	No. She had dermatomyositis	Anemia, thrombocytopeni, increased creatinine	ANA	PE	Died of respiratory failure on the 10th day

Steinberg, et al. 1971 [27]	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, thrombocyto-peni, consciousness alteration, schisto-cytes	ANA (n=1), RF (n=1)	GC	All died within 2 weeks

Note: ANA-Antinuclear Antibodies; CYC-Cyclophosphamide; GC-Glucocorticoid; IVIg-Intravenous Immunoglobulin; PE-Plasma Exchange; PRES-Posterior Reversible Encephalopathy Syndrome; RF-Rheumatoid Factor; SS-Sjögren's Syndrome; TTP-Thrombotic Thrombocytopenic Purpura.

ETHICAL APPROVAL

Ethics committee approval was deemed not necessary in our institutions for case reports. We declare that the paper has not been submitted elsewhere for publication. Patient consent has been obtained and that all reasonable steps have been taken to maintain patient confidentiality.

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CONFLICT OF INTEREST

Nothing to disclose.

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