Ref: Ro J Rheumatol. 2023;32(1)
DOI: 10.37897/RJR.2023.1.4

An unusual clue in the diagnosis of primary Sjogren's syndrome

Elena Juganaru[1], Claudia Cobilinschi[1,2], Ciprian Jurcut[3], Andreea Birlez[4], Daniela Opris-Belinski[1,2], Andra Balanescu[1,2]

[1]"Sf. Maria" Clinical Hospital, Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]"Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania
[4]Municipal Hospital, Ploiesti, Romania

ABSTRACT

Sjogren's syndrome (SSj) is a chronic autoimmune disease mainly targeting the exocrine glands, but sometimes associating extra-glandular manifestations. Xerosis, purpura, Raynaud's phenomenon, cutaneous vasculitis, annular erythema are the main forms of skin involvement.

A 26-year-old female patient was admitted for diffuse erythematous rash and angioedema, xerophthalmia and symmetrical arthralgia of hand joints. Anti-nuclear antibodies, anti-SSA and anti-Ro52 antibodies were identified, Schirmer's test was positive, thus the diagnoses of primary SSj and associated urticarial vasculitis were established. Treatment with oral methylprednisolone, azathioprine and hydroxychloroquine was initiated, with favourable response over the next week.

Patients with primary SSj that develop cutaneous vasculitis, lymphadenopathies or lymphopenia may be at risk for additional extra-glandular manifestations, including non-Hodgkin lymphoma.

Keywords: Sjogren syndrome, urticarial vasculitis, angioedema, immunosuppression

INTRODUCTION

Sjogren's syndrome (SSj) is a chronic autoimmune inflammatory disease primarily affecting the exocrine glands and leading to their functional impairment. Serum autoantibodies are present in the majority of patients with SSj and can be associated with specific clinical presentations, possibly contributing directly to the patients' phenotype [1].

Although SSj typically presents with xerophthalmia and xerostomia, a number of patients may develop extra-glandular manifestations. These include skin and joints, visceral organs, or the nervous system.

Among the cutaneous involvement, patients can present with skin dryness, annular erythema, cutaneous vasculitis, livedo reticularis or signs of lymphoproliferative transformation like nodular cutaneous amyloidosis [2].

Urticarial vasculitis (UV) is a rare presentation, exhibiting recurrent wheals persisting for more than a day and resolving with hyperpigmentation of the skin. It is difficult to differentiate from chronic idiopathic urticaria, however urticarial vasculitis injures small vessels, showing signs of leukocytoclastic vasculitis on histological examination. A number of conditions have been proven to trigger UV, such as drugs, infections but also associated autoimmune rheumatic diseases (SSj, systemic lupus erythematosus or rheumatoid arthritis). Moreover, UV can be the manifestation of a paraneoplastic syndrome, including haematological malignancies or colon adenocarcinoma [3].

Angioedema is a condition that can be potentially life-threatening and is classified as allergic, hereditary, acquired autoimmune or idiopathic. Acquired angioedema triggered by bradykinin is oftenly associated with the presence of antibodies against C1-inhibitor or increased use of C1-inhibitor in malignancies or autoimmune conditions [4].

Corresponding author:
Claudia Cobilinschi
E-mail: claudiadeaconu1@yahoo.com

Article History:
Received: 20 March 2023
Accepted: 27 March 2023

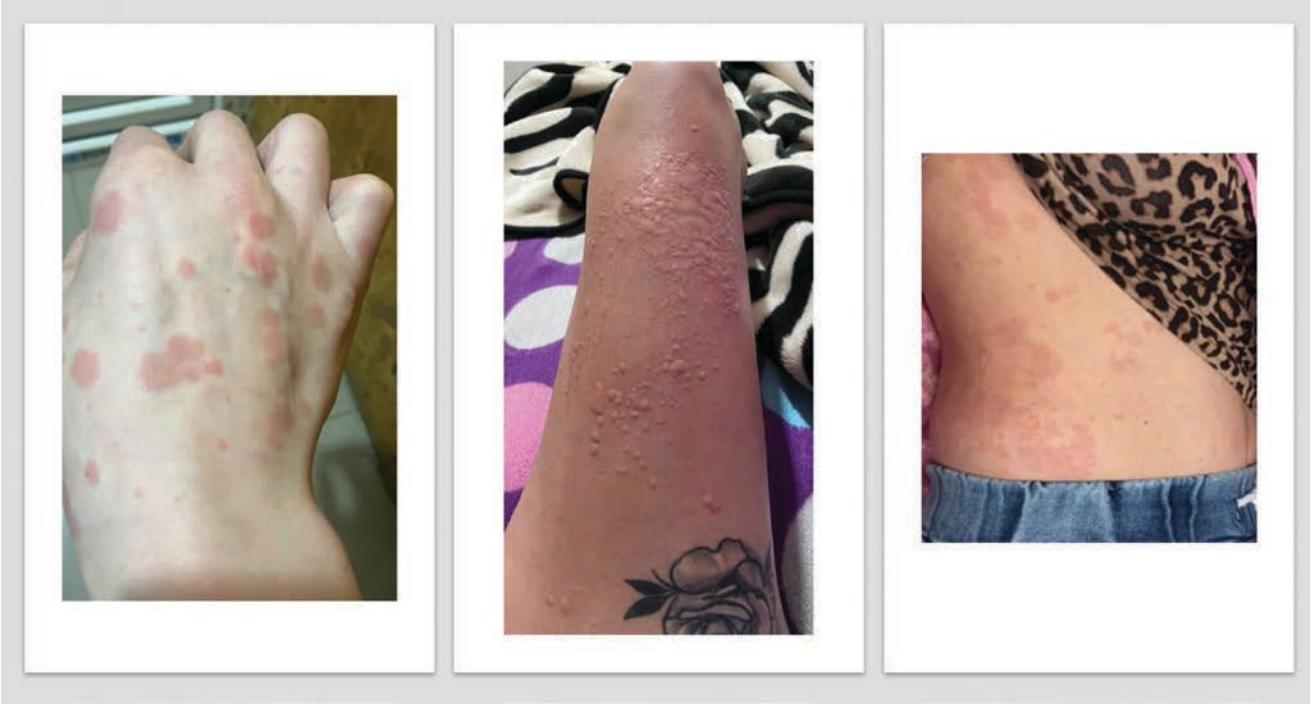

FIGURE 1. - Erythematous macular rash over the hands, trunk

We report a rare case of idiopathic angioedema, normocomplementaemic urticarial vasculitis and associated Sjogren's syndrome.

CASE PRESENTATION

A 26-year-old female patient, with no prior significant medical history was addressed to the Rheumatology Department for diffuse erythematous macular rash (Figure 1) and lip angioedema (Figure 2). Multiple intermittent episodes repeated over the last three months. She complained of recently installed xerophthalmia and arthralgia in small joints of the hands.

Physical examination confirmed non-pruritic indurated wheals over the upper and lower limbs and trunk (Figure 1) that lasted for more than 24 hours and resolved with local hyperpigmentation. Submandibular lymphadenopathies were identified but the patient denied fever, chills or recently confirmed infectious diseases. At the time of examination, she exhibited no peripheral arthritis.

Upon admission, she was under no chronic medication, no new food ingestion was mentioned and no significant family history regarding allergies.

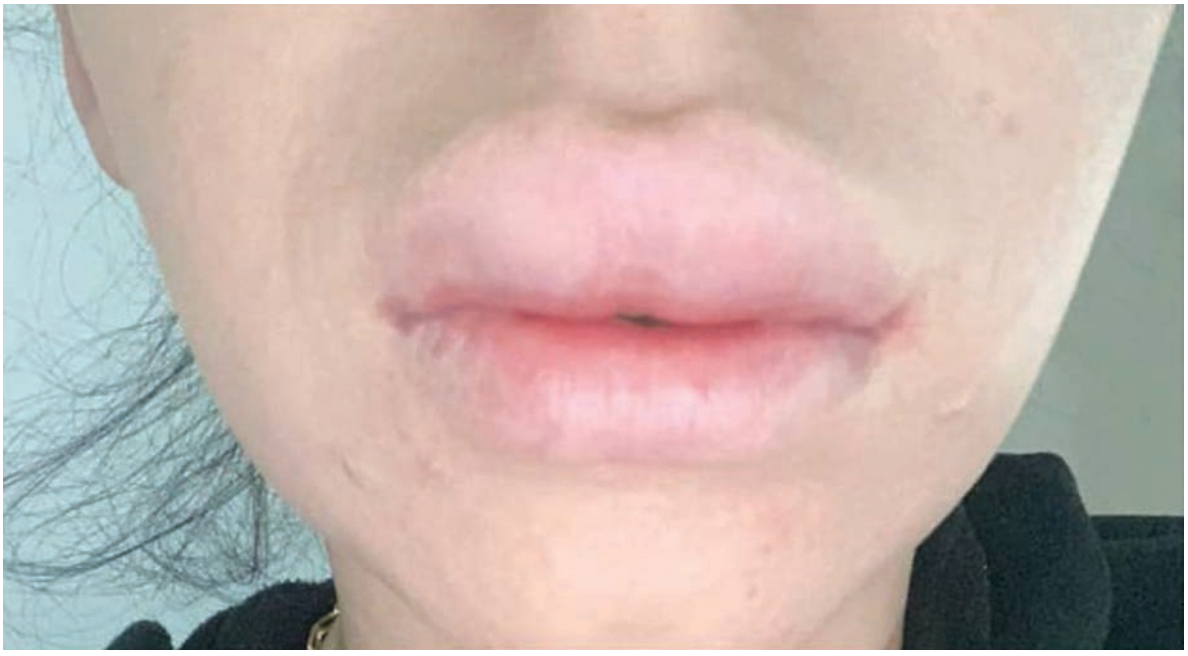

FIGURE 2. - Lip angioedema

Initial blood tests disclosed lymphopenia and elevated inflammatory markers (erythrocyte sedimentation rate ESR 38 mm/hour, C-reactive protein CRP 90 mg/dl, fibrinogen 490 mg/dl). Hypergammaglobulinemia with high IgG levels was confirmed by serum protein electrophoresis.

The immunological tests showed positivity of anti-nuclear (ANA), anti-SSA and anti-Ro52 antibodies. The rheumatoid factor RF, anti-citrullinated protein antibodies ACPA as well as c-ANCA and p-ANCA antibodies were negative. Complement fractions C1q and C4 were normal, while C3 was moderately lower than the reference value. Cryoglobulins were also tested and came back negative.

Ophthalmic examination confirmed an intensely positive Schirmer's test in both eyes. Additionally, salivary gland ultrasound described homogeneous glandular parenchyma with few areas of inhomogeneity without anechoic or hypoechoic areas, which corresponded to an OMERACT grey-scale scoring system for SSj of 0-1. Three submandibular lymphadenopathies were observed, the largest of them with a diameter of 1.5 cm.

Taking into consideration the clinical presentation (ocular dryness), the serological tests (positivity of anti-Ro/SSA antibodies, hypergammaglobulinemia, inflammatory syndrome), the ophthalmologic examination which confirmed the eye dryness, the diagnosis of primary Sjogren's syndrome was established, according to the ACR/ EULAR classification criteria, scoring 4 points.

The concomitant onset of rash, arthralgia and lymphadenopathies made the cutaneous manifestations to be further assessed in the clinical setting of the above diagnosis.

At the same time, extensive screening for infectious diseases was performed. Viral hepatitis, HIV infection, syphilis, Borrelia infection were excluded. In addition, thyroid function was assessed and thyroid hormone levels were optimal and anti-TPO and antithyroglobulin antibodies were negative. Further imagistic assessment including abdominal ultrasound and chest X-rays showed no particular features.

Since the common aetiologies for urticarial lesions, namely infections, medications, biting insects were ruled out and the screening for ANCA-associated vasculitides, autoimmune thyroid disease, systemic lupus erythematosus, rheumatoid arthritis turned out negative, SSj-associated cutaneous vasculitis was indicated as the most likely diagnosis. A skin biopsy was required in order to confirm the diagnosis, but the patient refused the procedure.

Once systemic involvement was excluded and the diagnosis of single-organ cutaneous small vessel vasculitis has been made, the treatment with oral methylprednisolone, azathioprine and hydroxychloroquine was initiated, with favorable response over the following weeks. Dapsone and colchicine were also considered but rapid resolution of muco-cutaneous lesions made them redundant at the time.

DISCUSSION

SSj may intricate with several skin findings, namely xerosis, purpura, Raynaud's phenomenon, cutaneous vasculitis or annular erythema that represent the most frequent forms of presentation [5]. Cutaneous vasculitis occurs in 4 to 10% of patients with primary SSj, with palpable purpura being the most common sign, but urticarial lesions or ulcerations are also possible. They are typically distributed over the lower extremities, while urticarial lesions may also be displayed over the arms, trunk or face. Urticarial vasculitis can be either normocomplementaemic or hypocomplementaemic, the latter being more frequent, as in the presented case. Both types may be associated with systemic symptoms such as angioedema or joint pain [6].

Evidence based data support the fact that skin vasculitis is more common in patients with anti-Ro and anti-La antibodies compared to patients with negative serology [7]. The high frequency of the association between cutaneous vasculitis and antibodies to the Ro/ SSA antigen imposes careful differential diagnosis between Sjogren-associated skin manifestations and purpura in the context of Waldenstrom's disease. The latter entity might be primary or secondary to SS or other pathologies. Even so, the clinical aspect of the red wheals and angioedema in our case is highly suggestive for hives.

The development of cutaneous vasculitis as well as lymphadenopathies or lymphopenia may represent additional risk factors for other extra-glandular manifestations, including lymphoma [8]. On the other hand, further predictors for developing lymphoma include low C4, serum beta2-microglobulin, splenomegaly, monoclonal immunoglobulins, rheumatoid factor which were absent in our patient [9].

Presence of cryoglobulins increases even more the risk of lymphoma, peripheral nerve and renal involvement, which makes it an important parameter to assess during future follow-up visits [10].

Antihistamines or non-steroidal anti-inflammatory drugs may be used in order to relieve symptoms, but treatment depends on the systemic involvement and the evolution of lesions over time. While normocomplementaemic urticarial vasculitis can resolve on its own, the hypocomplementaemic form often requires dapsone, colchicine, hydroxychloroquine or corticosteroids [11]. Up to present, there is no standard of care, but azathioprine, cyclophosphamide or cyclosporin may also be considered in case of refractory or severe disease.

CONCLUSIONS

The present case illustrates an unusual skin manifestation at Sjogren's syndrome onset. Cutaneous changes can be frequently overlooked because of the more prominent dryness symptoms. Even so, the increased risk of non-Hodgkin lymphoma or life-threatening vasculitis should be considered in the context of SSj. Certain clinical and paraclinical markers can be paramount tools for predicting the risk of complications in SSj and should be repeated during patient follow-ups.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Veenbergen S, Kozmar A, van Daele PLA, Schreurs MWJ. Autoantibodies in Sjögren's syndrome and its classification criteria. *J Transl Autoimmun.* 2022 Jan 1;5:100138.
2. Generali E, Costanzo A, Mainetti C, Selmi C. Cutaneous and Mucosal Manifestations of Sjögren's Syndrome. *Clin Rev Allergy Immunol.* 2017;53:3 [Internet]. 2017 Sep 4 [cited 2023 March 18];53(3):357–70. Available from: https://link.springer.com/article/10.1007/s12016-017-8639-y
3. Gu SL, Jorizzo JL. Urticarial vasculitis. *Int J Womens Dermatol.* 2021 Jun 1;7(3):290–7.
4. Christiansen J, Kahn R, Schmidtchen A, Berggård K. Idiopathic angioedema and urticarial vasculitis in a patient with a history of acquired haemophilia. *Acta Derm Venereol* [Internet]. 2015 [cited 2023 March 18];95(2):227–8. Available from: https://pubmed.ncbi.nlm.nih.gov/24923420/
5. Soy M, Piskin S. Cutaneous findings in patients with primary Sjogren's syndrome. *Clin Rheumatol* [Internet]. 2007 Aug [cited 2023 March 18];26(8):1350–2. Available from: https://pubmed.ncbi.nlm.nih.gov/16915358/
6. Urticarial Vasculitis: Background, Pathophysiology, Etiology [Internet]. [cited 2023 March 18]. Available from: https://emedicine.medscape.com/article/1085087-overview
7. Scofield RH. Vasculitis in Sjögren's Syndrome. *Curr Rheumatol Rep* [Internet]. 2011 Dec [cited 2022 Dec 23];13(6):482. Available from: /pmc/articles/PMC5278618/
8. Ramos-Casals M, Anaya JM, García-Carrasco M, Rosas J, Bové A, Claver G, et al. Cutaneous vasculitis in primary Sjögren syndrome: classification and clinical significance of 52 patients. *Medicine* [Internet]. 2004 Mar [cited 2022 Dec 23];83(2):96–106. Available from: https://pubmed.ncbi.nlm.nih.gov/15028963/
9. de Vita S, Gandolfo S. Predicting lymphoma development in patients with Sjögren's syndrome. *Expert Rev Clin Immunol* [Internet]. 2019 Sep 2 [cited 2022 Dec 23];15(9):929–38. Available from: https://pubmed.ncbi.nlm.nih.gov/31347413/
10. Quartuccio L, Baldini C, Priori R, Bartoloni E, Carubbi F, Alunno A, et al. Cryoglobulinemia in Sjögren Syndrome: A Disease Subset that Links Higher Systemic Disease Activity, Autoimmunity, and Local B Cell Proliferation in Mucosa-associated Lymphoid Tissue. *J Rheumatol* [Internet]. 2017 Aug 1 [cited 2023 March 18];44(8):1179–83. Available from: https://www.jrheum.org/content/44/8/1179
11. Buck A, Christensen J, McCarty M. Hypocomplementemic Urticarial Vasculitis Syndrome: A Case Report and Literature Review. *J Clin Aesthet Dermatol* [Internet]. 2012 Jan [cited 2023 March 18];5(1):36. Available from: /pmc/articles/PMC3277093/