



Case report

Parallel ocular and serologic course in a patient with early Sjogren's syndrome markers

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ARTICLE INFO

Article history:

Received 25 January 2017

Received in revised form

1 August 2017

Accepted 2 October 2017

Available online 6 October 2017

Keywords:

Dry eye syndrome

Novel autoantibodies

Serological conversion

Sjogren's syndrome

Anti-SSA/Ro and anti-SSB/La

ABSTRACT

Purpose: To report on a case of a young female with progressing dry eye symptoms and evolving autoimmune markers consistent with a presentation of early Sjogren's syndrome (SS).

Observations: A 32 year-old female presented with chronic dry eye symptoms refractory to artificial tears. Slit lamp examination revealed punctate epithelial erosions, decreased tear break-up time, and decreased tear lake bilaterally. Initial tests for ocular surface inflammation (InflammaDry, Quidel, San Diego) and systemic autoantibodies (antinuclear antibodies, anti-SSA/Ro and anti-SSB/La) were negative. After 4 months of persistent ocular symptoms and signs, ocular surface inflammation was detected via InflammaDry and blood results included a positive antinuclear antibody (1:160), rheumatoid factor (IgG 25.3 EU/ml), and carbonic anhydrase 6 (IgM 20.2 EU/ml), but persistently negative anti-SSA/Ro and anti-SSB/La antibodies.

Conclusions and importance: Taken together, these findings were suggestive of early Sjogren's syndrome with simultaneous appearance of both ocular and serum biomarkers. Novel autoantibodies testing in suspected patients can guide early intervention and potentially improve both the glandular and extraglandular function in patients.

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1. Introduction

Sjogren's syndrome (SS) is a chronic autoimmune disease characterized by hallmark symptoms of oral and ocular dryness due to lymphocytic destruction of exocrine glands. It is one of the three most common autoimmune disorders, affecting 0.5–4% of the population with more than 2 million Americans living with the disease.^{1–3} Despite its high prevalence, SS continues to be underdiagnosed due to its nonspecific symptoms, variable clinical presentations and lack of standardized diagnostic criteria. While the most widely used criteria is by the American-European Consensus Group (AECG),⁴ the most current classification criteria adopted by the American College of Rheumatology⁵ is based on data from the Sjogren's International Collaborative Clinical Alliance (SICCA) and defines SS by the presence of at least 2 out of the following 3 objective findings:

- 1) Positive serum anti-SSA (Ro) and/or anti-SSB (La) or [positive rheumatoid factor (RF) and antinuclear antibody (ANA) \geq 1:320]
- 2) Ocular staining score \geq 3
- 3) Presence of focal lymphocytic sialadenitis with focus score \geq 1 focus/4mm² in labial salivary gland biopsies

Both the older and newer criteria place emphasis on the presence of anti-SSA/Ro and anti-SSB/La in the diagnosis of SS, yet it is known that both markers are found late in the disease process and are only present in 30–60% and 20–40% of SS patients, respectively.^{3,6–11} Many patients are thus misdiagnosed until more severe complications of SS develop, such as destruction of exocrine glands, lung and kidney diseases, and B cell lymphoma. On average, patients experience symptoms for 3.9 years before being diagnosed with SS, during which time they can be subjected to ongoing tissue damage and psychological distress from unexplained symptoms.¹² In fact, it is the late diagnosis that may contribute to the lack of efficacy of several treatments that have been tested in SS,^{13–21} which may have been effective if started earlier in the disease course. Recently, studies have reported on new autoantibodies

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against carbonic anhydrase VI (CA6), salivary protein 1 (SP1), and parotid secretory protein (PSP), which have been found in mice and earlier in the course of SS in humans.^{7,8,10} However, previous cases have only retrospectively demonstrate the presence of these antibodies in patients with long-standing disease and it is not clear how these antibodies are related to the course of ocular disease in SS. Herein, we report a case of a female with newly evolving ocular disease, whose systemic markers mirrored the course of her ocular disease.

2. Case report

A 32 year-old female presented with sensations of dryness and discomfort in both eyes that had been ongoing for seven months. The patient stated that artificial tears provided minimal relief and that applying pressure over the eyes alleviated the pain transiently. She also endorsed mild fatigue and malaise, but denied blurry vision, oral dryness or joint pain. Her past medical history was significant for a right-sided Bell's palsy with subsequent development of misdirected innervation from CN V to VII (Marin Amat syndrome) and blepharospasm for which she received botulinum toxin injections. She also endorsed chronic headaches, which were also treated with botulinum toxin. Her past surgical, family and social histories were noncontributory; the patient did not take any medications or supplements, and reported no known allergies.

On her first visit, uncorrected visual acuity was 20/20 in both eyes. Intraocular pressures were 12 mm Hg in the right eye and 11 mm Hg in the left eye and pupils were equal, round and reactive to light. Confrontational visual fields were full and extraocular motility testing was within normal limits. External examination revealed facial asymmetry without lagophthalmos but with decreased orbicularis tone in the right versus left eyelid. Anterior segment exam revealed trace bulbar injection in both eyes, linear erosions in the right eye, mild inferior punctate epithelial erosions in both eyes, and decreased tear lake bilaterally (Fig. 1). Dry eye testing included a dry eye questionnaire-5 (DEQ5) score²² of 13 out of 22, decreased tear break-up time (TBUT) (2 seconds right eye, 3 seconds left eye), and decreased tear production in the right eye (anesthetized Schirmer's 5 mm wetting right eye and 18 mm wetting left eye at 5 minutes) (Table 1). InflammDry testing (Quidel, San Diego, CA) was negative for the presence of matrix metalloproteinase 9 (MMP-9) on the ocular surface in both eyes.²³ Of note, InflammDry is an in-office test that detects levels of MMP-9 via antibody-antigen interaction (lower detection limit 40ng/ml). The result window reads positive with two lines (one blue and one pink) and negative with one line (only blue). The test provides a qualitative (yes/no) response but the intensity of the pink line is directly related to the amount of MMP-9 present. Dilated fundus examination of the macula, vessels and periphery

was within normal limits. Given the low tear lakes, an ANA panel was ordered and returned negative (<1:40).

On follow up 4 months later, vision remained 20/20 in both eyes. Repeat dry eye testing revealed persistent severe DE symptoms (DEQ5 = 15), slightly improved TBUT (8 seconds right eye, 3 seconds left eye), stable corneal staining (3 right eye, 2 left eye, graded based on the Bron scale²⁴), and low tear production (anesthetized Schirmer's 2 mm right eye, 7 mm left eye at 5 minutes) (Table 1). InflammDry testing on this occasion returned moderately positive for the presence of MMP-9 on the ocular surface of both eyes (Fig. 2). At this time, an expanded SS panel revealed conversion to an ANA titer of 1:160 and multiple elevated autoantibodies including RF IgG at 25.3 EU/ml, CA6 IgM at 20.2 EU/ml (normal <20 EU/ml for both), and RF IgM at 18.3 EU/ml (normal <10 EU/ml) (Table 1). Of note, anti-SSA/Ro and anti-SSB/La levels were within normal limits (5.8 EU/ml and 2.5 EU/ml, respectively). Based on these findings, the patient was started on fluorometholone 0.1% in conjunction with cyclosporine emulsion 0.05% twice a day in both eyes.

She reported initial improvement in symptoms but discontinued the medications 1 month later after discovering that she was pregnant. On repeat testing 3 months later, despite persistent severe DE symptoms, improved ocular surface parameters were noted and no inflammation was detected by InflammDry (Table 1). A repeat autoantibody panel at this time found slight increases in several autoantibodies (CA6 IgM, PSP IgA, PSP IgM, SP1 IgG, and SP1 IgM), although only the CA6 IgM level remained above normal limits (Table 1).

3. Discussion

To summarize, we describe a patient with persistent dry eye symptoms whose ocular and serological abnormalities developed concurrently, with new inflammation detected on the ocular surface at the same time that IgM serologies were positive for early SS markers. While the patient's history of right-sided Bell's palsy likely played a role in her presentation, the presence of bilateral corneal staining, younger age, and systemic symptoms suggest an autoimmune component to her disease. By current definitions, our patient does not meet criteria for SS with only 1 of 3 positive signs (corneal staining) as the current ANA threshold is $\geq 1:320$ and the newer antibodies are not part of the SS criteria. Yet, her clinical examination and serologic conversion (anti CA6 IgM positivity and increasing levels of other novel autoantibodies) fit in with the diagnosis of early SS.

Carbonic anhydrase VI (CA6), parotid secretory protein (PSP) and salivary protein 1 (SP1) autoantibodies were first detected as potential early markers of SS in studies utilizing the interleukin 14 alpha transgenic mouse (IL14 α TG) that develops many features of SS in the same relative time frame as SS patients.⁷ Subsequently,

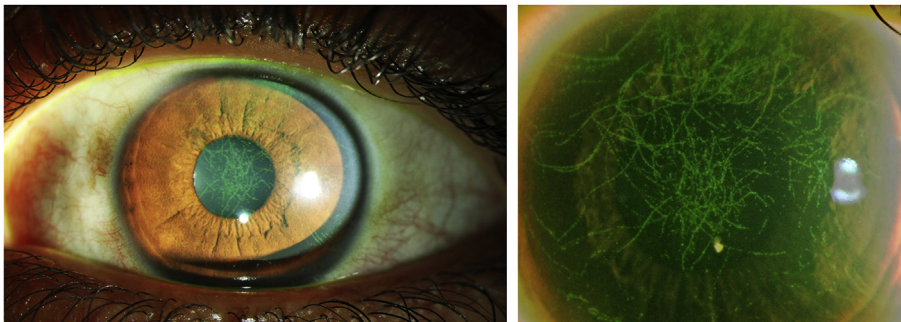


Fig. 1. Slit lamp photograph of the right eye depicting linear erosions in the central cornea.

Table 1
Course of patient's ocular and systemic findings.

	Initial visit	4 month follow-up	8 month follow-up	Reference values
DEQ5	13	15	17	
TBUT, seconds OD, OS	2, 3	8, 3	8, 8	
Corneal staining, OD, OS	3, 2	3, 2	2, 2	
Schirmer's, mm wetting at 5 minutes OD, OS	5, 18	2, 7	11, 10	
InflammaDry	Negative OU	Positive OU	Negative OU	
ANA titer	<1:40	1:160		<1:40
RF IgG		25.3		<20 EU/ml
RF IgA		11.8		<20 EU/ml
RF IgM		18.3		<10 EU/ml
SS-A(Ro)		5.8		<20 EU/ml
SS-B(La)		2.5		<50 EU/ml
CA6 IgG		9.2	2.4	<20 EU/ml
CA6 IgA		10.7	2.6	<20 EU/ml
CA6 IgM		20.2	21.9	<20 EU/ml
PSP IgG		4.3	4.3	<20 EU/ml
PSP IgA		<1.0	6.1	<20 EU/ml
PSP IgM		3.2	6.2	<20 EU/ml
SP1 IgG		3.1	5.3	<20 EU/ml
SP1 IgA		7.9	3.6	<20 EU/ml
SP1 IgM		14.9	17.3	<20 EU/ml

Abbreviations: ANA, antinuclear antibody; CA6, carbonic anhydrase VI; DEQ5, dry eye questionnaire-5; OD, right eye; OS, left eye; OU, both eyes; PSP, parotid secretory protein; RF, rheumatoid factor; SP1, salivary protein 1; TBUT, tear break-up time. Abnormal values are in bold.



Fig. 2. The InflammaDry test (Quidel, San Diego, CA) reveals a moderate-strength pink band that correlates with the presence of inflammation (i.e. matrix metalloproteinase-9) on the ocular surface. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

their presence was confirmed in humans and shown to appear prior to the development of anti-SSA/SSB.^{7,8,10} For example, in patients with early SS, more than 65% expressed one of the novel antibodies while only 20–30% expressed antibodies for SSA/SSB.^{7,10} In patients with late SS, the relationship reversed with 62–80% positive for SSA/SSB and 40–70% positive for novel autoantibodies.^{6,7,10} Many autoimmune profiles have been described, however, and there are SS patients that lack SSA/SSB but express SP1 antibodies even late in the disease.^{7,8} Furthermore, anti-SSA/SSB antibodies are not specific for SS and are found in other autoimmune disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), primary biliary cirrhosis (PBC) and connective tissue diseases. In contrast, SP1 and CA6 antibodies appear more specific and are rarely found in normal individuals (less than 5%) or in RA patients lacking secondary SS.⁷ These findings may be due to the fact that SP1 and CA6 antigens are found selectively in salivary and lacrimal glands compared to Ro and La, which are found in virtually all cells.¹⁰ It is likely that an inciting infection of the salivary or lacrimal glands releases these proteins, triggering

the production of autoantibodies and development of SS in genetically susceptible individuals. Overall, these studies have shed light on the importance of these novel antibodies in the diagnosis of SS, leading to the development of a new commercially available diagnostic tool, the Sjög test (Bausch & Lomb, Rochester, NY, USA), which incorporates both traditional and novel autoantibodies on its panel.²⁵

Several agents with activity against RA and SLE have been evaluated in Sjogren's syndrome including corticosteroids, piroxicam, hydroxychloroquine, antimetabolites (azathioprine), androgens (dehydroepiandrosterone sulfate), doxycycline, and anti-TNF agents (infliximab, etanercept). While some provided symptomatic relief, none improved histological abnormalities or exocrine gland function.^{13–17,19–21,26–28} The ineffectiveness of current treatments may be attributed to the fact that most therapeutic trials are conducted in patients with late stage SS where many patients already have extra-glandular manifestations of the disease (e.g. thyroiditis, lung disease, kidney disease, vasculitis, neuropathy, lymphoma). Rituximab has been the best-studied therapy with mixed results.

Initially, a randomized controlled study of 17 SS patients with positive anti-SSA/SSB and score of >50 on a 100mm fatigue visual analogue scale (VAS) showed benefit to rituximab/prednisolone over placebo/prednisolone in improving fatigue and quality of life.²⁶ Subsequently, improved salivary flow rates, sicca symptoms and fatigue were found using a similar rituximab regimen.²⁸ Most recently, a third randomized controlled trial failed to meet its primary end point of improved global disease, pain, fatigue or dryness after 24 weeks of treatment, but did show some improvement in fatigue at earlier time points.²⁷ Abatacept (which inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28) has also been shown to decrease disease activity and fatigue in SS patients with disease duration of less than five years.²⁹ However, no effect on salivary or lacrimal gland function was noted,²⁹ suggesting that perhaps the “window of opportunity” for improved gland function had passed.

The idea of a “window of opportunity”, i.e. that an identical treatment regimen provides superior benefit if started early versus late in a disease course, has been well described in RA with slowed radiographic progression^{30–32} and low or no disease activity^{31–35} more likely if a medication is started earlier in the disease. It is possible that a similar paradigm exists in SS. It is interesting that in our patient, after 1 month of local anti-inflammatory therapy, no inflammation was detected on the ocular surface 3 months later, despite persistent dry eye symptoms.

Our findings need to be considered bearing in mind limitations for this case. For example, a labial salivary gland biopsy (LSGB) was not performed in our patient. While LSGB has been shown to have high sensitivity, specificity, positive and negative predictive values,³⁶ its usefulness early in the course of disease is not as well established. To summarize, this case highlights the complexities involved in making a diagnosis and treating SS. Currently, the best management approach for patients such as ours is not known and as such, data are needed to determine if early intervention (with topical and/or systemic therapy) will improve glandular and extra-glandular function in the long-term.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Financial support

Supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research EPID-006-15S, R01EY026174 (Dr. Galor), NIH Center Core Grant P30EY014801 and Research to Prevent Blindness Unrestricted Grant.

Conflict of interest

The following authors have no financial disclosures: (LP, RG, JD, LY, DA, AG, IL).

Authorship

Authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgments

None.

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