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# Xerophthalmia of Sjogren's Syndrome Diagnosed with Anti-Salivary Gland Protein 1 Antibodies

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## Key Words

Xerophthalmia · Sjogren's syndrome · Autoantibodies

## Abstract

**Purpose:** The purpose of this report is to describe 2 patients with persistent severe dry eyes, positive Schirmer tests for Sjogren's syndrome (SS) but lacking antibodies to either Ro or La. These patients were diagnosed to have SS by detecting antibodies to salivary gland protein 1 (Sp1) and parotid secretory protein (PSP). This report emphasizes the existence of patients with SS who lack antibodies to either Ro or La and may therefore be misdiagnosed. Detection of novel autoantibodies, including antibodies to Sp1 and PSP, are helpful in identifying these patients. Initial presentation may simply be dry eyes. **Methods:** Two patients who presented to our ophthalmology clinic are described. One of the patients underwent multiple procedures over a period of 10 years for severe xerophthalmia. The other patient had rheumatoid arthritis and xerophthalmia. However, in both patients, chronic xerophthalmia had been considered to be idiopathic because antibodies Ro and La were negative. Further serologic testing revealed antibodies to Sp1 and PSP. **Results:** Two patients who lacked antibodies to Ro and La but not to Sp1 and PSP were diagnosed as having SS. **Conclusion:** Patients presenting with unexplained dry eyes may not always show the serology markers in the current criteria for SS, anti-Ro and anti-La. In these cases, investigation for novel, early antibodies to Sp1 and PSP is of importance in the diagnosis of SS.

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## Case Descriptions

### Case 1

A 53-year-old Caucasian female with complaints of dry eyes and a burning sensation in the eyes presented to our ophthalmology clinic 5 years ago. Her medical history revealed that the symptoms had persisted for 10 years, with some relief with lubricating eye drops used every 0.5–1 h. Prior serology studies for antinuclear antibodies (ANA), Ro and La were all negative. She denied any symptoms of dryness of her mouth, and she had no other comorbidities. There was no family history of autoimmune diseases.

Clinical examination showed dry eyes, with slit lamp examination revealing thickening and hyperemia of the eyelids. Schirmer's test was very low at 3 mm in each eye. Her laboratory evaluation included a normal complete blood count and a comprehensive metabolic profile. ANA, anti-Ro and anti-La were all negative. She was put on GenTeal gel alternating with artificial tears (Restasis eye drops) four times/day. During the course of the next 5 years, she underwent multiple surgeries for persistent eye dryness, including three procedures of silicone punctal plug placement in each eyelid, permanent thermal punctal occlusion, and later, resection of the canaliculus due to repeat reopening of the punctum despite three permanent thermal occlusions and continued patient discomfort secondary to refractory dryness of the eyes. Additional evaluation to determine the etiology of dry eyes was done. It revealed the presence of antibodies to salivary gland protein 1 (Sp1) and parotid secretory protein (PSP), leading to the diagnosis of Sjogren's syndrome (SS).

### Case 2

A 68-year-old Caucasian female with a known history of rheumatoid arthritis (RA) presented to our ophthalmology clinic with complaints of persistent dry eyes and irritation for the last 25 years. She had tried artificial tears, Restasis eye drops and GenTeal gel with some relief. Her prior workup by her rheumatologist included antibodies to Ro and La, which were both negative. Her medications included methotrexate for her RA for the last 30 years.

On physical evaluation, she was noted to have dry eyes. Slit lamp examination revealed hyperemia and thickening of the eyelids. Schirmer's test was very low at 1mm in both eyes. Her laboratory evaluation in our clinic included antibodies to Ro and La that were negative and antibodies to ANA and rheumatoid factor, which were both positive. Evaluation of additional autoantibodies revealed the presence of antibodies to Sp1 and PSP, leading to the diagnosis of SS. Antibody testing for Sp1 and PSP in both patients was done at Immco Diagnostic Laboratory, Buffalo, N.Y., USA.

## Discussion

SS is an autoimmune disease starting in the lacrimal and salivary glands but with eventual systemic involvement of multiple other organs. SS can also occur secondary to other autoimmune diseases such as lupus and RA, known as secondary SS. Patients with SS typically present with a dry, gritty sensation in the eyes and a dry mouth. At this stage, there has already been significant destruction of the salivary and lacrimal glands. Typically, involvement of the lachrymal and submandibular glands occurs before involvement of the parotid glands. Due to this, the presentation of dry eyes may occur much earlier in the disease process and precede the presence of a dry mouth. Lung and kidney disease tend to

occur late in the disease process. About 5% of the patients with SS develop B cell lymphoma, most commonly occurring in the salivary glands and gastrointestinal tract [1–3].

The diagnostic criteria for SS include clinical criteria: a Schirmer test with a result of <5 mm of wetting/5 min or a Rose Bengal score of >4 (van Bijsterveld) as well as ocular and oral symptoms. Daily persistent dry eyes for more than 3 months, use of lubricants more than 3 times/day, a recurrent feeling of sand or gravel in the eyes as well as a dry mouth for more than 3 months with a glass of water required to eat dry foods further support a diagnosis of SS [4]. In our clinics, the limit for Schirmer's test is set at 3 mm to reduce positive results in the normal population to <15% [5]. Histological criteria for SS include focal sialoadenitis, and serological criteria include ANA, RF and antibodies to Ro and/or La [6]. The diagnosis of SS is excluded if there is a history of head and neck radiation treatment, hepatitis C, AIDS, lymphoma, sarcoidosis, graft versus host disease or anticholinergic drugs. The 2 patients described in this case report met the clinical criteria for SS based on dry eyes and a positive Schirmer test but lacked antibodies to Ro or La.

The autoantibodies that are most commonly believed to be associated with SS are Ro and/or La antibodies. Ro (SS-A) is an extractable nuclear antigen that is composed of proteins 52 kD and 60 kD combined with cytoplasmic RNA species [1, 6]. Antibodies to Ro are found in patients with autoimmune mediated systemic connective disorders including SS. Antibodies to Ro are detected in 40–60% of the patients [1, 6, 7]. La (SS-B) is a 48-kD protein and an extractable nuclear antigen. Antibodies to La are detected in <20% of the patients but they are highly specific to SS [6, 7]. However, there are multiple other antibodies being studied, including antibodies to muscarinic receptor 3, tissue kallikrein, alpha-fodrin, carbonic anhydrase II and VI, PSP and Sp1. The significance of these autoantibodies has not been fully appreciated [7–15].

Animal models have been used extensively to study SS. One of the mouse models used to study SS is the interleukin 14 alpha transgenic (IL14 $\alpha$ TG) mouse. It reproduces all events noted to occur in SS patients in the same relative time frame [16–18]. The use of this animal model led to the discovery of the novel autoantibodies in SS. These include antibodies to Sp1, carbonic anhydrase 6 (CA6) and PSP. The presence of these autoantibodies in the sera of patients with SS has been confirmed [15]. As per these studies, only 25% of the IL14 $\alpha$ TG mice developed Ro and/or La antibodies. Interestingly, the time course in the development of the autoantibodies showed that the Sp1 and CA6 antibodies were present very late in the disease [15].

The clinical presentation of both patients was very typical of SS. Our first patient had symptoms of dry eyes requiring multiple procedures to help control them. Our second patient had dry eyes for many years along with the comorbidity of RA. However, a diagnosis of SS was not made in either of our patients due to the lack of Ro and/or La antibodies. The detection of Sp1 and PSP antibodies in our patients led to the diagnosis of primary SS in the first and secondary SS in the second patient.

These cases stress the importance of using autoantibodies besides Ro and La in the diagnosis of SS. Further studies are in progress to define whether antibodies to Sp1 and PSP not only define early stages of SS but also particular forms of SS. Early diagnosis of SS is critical for the development of improved forms of therapy.

#### Disclosure Statement

Both J.L.A. Jr., MD, and L.S., PhD, participated in the discovery of the autoantibodies to SP1 and PSP. The SUNY at Buffalo School of Medicine holds a patent on these autoantibodies

that is licensed to Immco and Nicox. J.L.A. Jr. and L.S. receive royalties through this licensing agreement. L.S. and K.M. work for Immco Diagnostics.

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