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Sjögren's Syndrome: More Than Just Dry Eye

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Abstract

Purpose: Sjögren's syndrome (SS) is a common autoimmune disease affecting about four million Americans. Although approximately 1 in 10 patients with clinically-significant aqueous deficient dry eye has underlying SS, widespread underappreciation of SS leads to significant underdiagnosis, delays in diagnosis, and consequent morbidity and mortality. The purpose of this article is to illustrate that in addition to dry eye, SS can cause serious, vision-threatening extraglandular ocular manifestations.

Methods: We conducted a narrative review of studies that have examined the dry eye and extraglandular ocular complications of SS.

Results: SS-related dry eye is a progressive condition with major negative impact on the quality-of-life of afflicted patients, not only due to symptoms of ocular discomfort but also visual dysfunction. In addition, SS can lead to corneal melt/perforation, uveitis, scleritis, retinal vasculitis, and optic neuritis. A major problem with currently-available SS disease activity measurement instruments is the lack of domains evaluating dry eye-related visual dysfunction. For example, one of the most commonly-used instruments for assessing patient symptoms in SS (the EULAR Sjögren's Syndrome Patient Reported Index [ESSPRI]) only includes one item (out of three) that addresses the severity of overall dryness, without mention of dry eye symptoms or vision-related quality-of-life. Similarly, no extraglandular ocular complications are included in currently-available SS disease activity instruments (e.g., the EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI]).

Conclusions: There needs to be a paradigm shift in which eye care providers and rheumatologists become more familiar with various SS-related extraglandular ocular manifestations. Existing disease activity measurement instruments must incorporate dry eye symptoms, particularly those related to visual dysfunction. An evidence-based screening algorithm for determining which patients with dry eye should be tested for underlying SS may be particularly helpful in preventing delays in diagnosis.

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Keywords

Sjögren's syndrome; dry eye; extraglandular symptoms; underdiagnosis

Sjögren's syndrome (SS) is a common autoimmune disease that affects approximately 4 million Americans.[1] SS manifests as chronic and debilitating inflammation that is mediated by autoantibody production and lymphocytic infiltration and, ultimately, causes permanent destruction of exocrine glands,[2] resulting in sicca symptoms, such as dry eye and dry mouth. SS was first described in 1933 by Dr. Henrik Sjögren,[3] a Swedish ophthalmologist, who reported 19 women with severe dry eye and dry mouth who also had lymphocytic infiltration of lacrimal and salivary glands, as well as systemic manifestations.

OBSERVATIONS

Although sicca symptoms are the sine qua non and most bothersome symptoms of SS, systemic consequences, such as visceral organ involvement, malignancies, peripheral neuropathy, myelitis, and meningitis, are common as well.[4–7] A 2014 systematic review found that compared with the general population, SS was associated with an increased risk of any cancer (relative risk [RR], 1.5; 95% confidence interval [CI], 1.2–1.9), non-Hodgkin lymphoma (RR, 13.8; 95% CI, 8.5–19.0), and thyroid cancer (RR, 2.6; 95% CI, 1.1–4.0).[5] Indeed, SS is an independent risk factor and the autoimmune disease most frequently associated with lymphoma.[6–13]

Dry eye affects approximately 8% of the more than 108 million Americans older than 50 years; approximately 1 in 10 of these patients with dry eye has underlying SS.[14] However, underlying SS remains undiagnosed in two-thirds of those patients with dry eye who have SS and are seen in eye clinics.[2,15,16] Even in the one-third of patients in whom the diagnosis is made, the average time from onset of dry eye symptoms to diagnosis of SS is about a decade.[17,18]

Various factors have led to this significant underdiagnosis and delayed diagnosis of SS in patients with dry eye. First, SS is a complex disease with diverse symptoms involving various organs and systems in the body. Second, dry eye is highly prevalent and multifactorial, making it challenging to identify patients with underlying SS. There is a lack of evidence-based, validated screening tools or algorithms to determine which patients with dry eye should be worked up for SS. Third, there is widespread underappreciation of the importance of SS among eye care providers, leading to underreferral for systemic workups. In a recent survey of ophthalmologists, approximately half reported that they refer fewer than 5% of patients for SS workup; approximately 1 in 5 ophthalmologists reported never referring any patients.[19] Systemic inflammatory diseases are common in patients with clinically significant aqueous-deficient dry eye, and a majority of those patients have underlying SS with no previous diagnosis.[20]

SS-related dry eye is a progressive condition that has a major negative impact on the quality of life of afflicted patients. On a daily basis, patients with SS experience significant vision fluctuation with blinking, blurred vision, eye fatigue, and difficulty with reading, despite

perfect visual acuity.[18,21,22] This difficulty with reading has a negative impact on employment and workplace productivity, particularly in individuals who work in desk jobs. Although patients with SS-related dry eye have generally higher ocular surface staining scores, they have less severe symptoms of ocular discomfort than patients with non–SS-related dry eye.[23,24] However, patients with SS-related dry eye have a greater degree of visual difficulty. The reason for this paradox is unknown, but reduced ocular discomfort may be related to reduced corneal sensation in the setting of advanced ocular surface dryness and inflammation.[25] Therefore, routine ocular surface evaluations should be performed in all patients with SS-related dry eye, even in the absence of symptoms.

A major problem with currently available SS disease activity measurement instruments is that they do not include any domains specific to dry eye. For example, one of the most commonly used instruments for assessing patient symptoms in SS (the EULAR Sjögren's Syndrome Patient Reported Index [ESSPRI][26]) includes only 1 item (of 3) that addresses the severity of dryness, specifically overall dryness and not ocular dryness. The other 2 items address the severity of fatigue and pain (in the arms or legs). Patients are asked to focus on the previous 2 weeks and rate each of the 3 items on a scale of 0 (absence of the symptom) to 10 (maximal possible severity of the symptom).[26] A large survey of patients with dry eye due to SS revealed that they rate dry eye as considerably more important than dryness of the mouth.[27] Therefore, there is a critical need for inclusion of items that specifically capture symptoms of ocular dryness, particularly in relation to impairment of visual function.

In addition, SS can lead to serious ocular manifestations, such as decreased vision or even blindness (Table 1). Patients with SS often develop inflammation of the ocular surface, such as chronic conjunctivitis, sterile keratolysis, and nonhealing corneal ulcers (Fig. 1).[17,28–33] Inflammation of other parts of the eye, such as uveitis,[17,34,35] scleritis (Fig. 2),[17,36–38] retinal vasculitis,[17] and optic neuritis,[17] has also been reported. In a large, tertiary care–based longitudinal cohort study, extraglandular ocular manifestations were present in more than 1 in 3 patients with SS, and 13% had vision-threatening findings.[17] In addition, compared with patients without vision-threatening extraglandular ocular findings, patients with such findings were much more likely to develop life-threatening systemic complications.[17] Systemic immunosuppressive agents are commonly initiated in patients with systemic complications.[39] Because most eye care providers are not sufficiently trained to appropriately prescribe these agents and monitor these patients, prompt referral to rheumatology clinics is essential. Regrettably, none of these extraglandular ocular complications are included in currently available SS disease activity instruments (eg, the EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI][40]). The ESSDAI includes 12 domains representing 12 organ systems (cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematologic, glandular, constitutional, lymphadenopathic, and biological), with each domain assessed for different levels of disease activity.[40] The ESSDAI has been used commonly when assessing the effectiveness of systemic immunosuppressive or immunomodulatory treatments for systemic complications of SS. However, the use of these agents for ocular complications is much less recognized.[39] It is critical that future revisions of the ESSDAI and other disease activity measures include an assessment of ocular complications.

Underappreciation of the significance of eye disease in SS is further demonstrated by examining the classification criteria for SS. For example, in the 2012 American College of Rheumatology (ACR) SS classification criteria, the ocular staining score was assigned equal weight as the other 2 criteria (positive labial salivary gland biopsy and serology).[41] However, more recently, the ACR and EULAR put forth a new set of SS classification criteria.[42] In this set of criteria, the presence of a positive labial salivary gland biopsy and a positive SS antibody are each weighted 3 times as heavily as the ocular examination findings (ocular surface staining or Schirmer test).[42] Given the absence of available evidence-based screening tools for patients with dry eye, clinicians often use these classification criteria as a guide when deciding which patients should be referred for systemic workups. Because the ocular criteria are weighted less than the other criteria, clinicians may underestimate the importance of the presence of these ocular findings, thereby continuing to contribute to the patterns of underreferral for systemic workups for SS.

CONCLUSIONS

Because patients with undiagnosed SS often present with symptoms of dry eye, eye care providers have the opportunity and responsibility to significantly reduce delays in diagnosis and improve the quality of life of patients by timely referral for systemic workups. There needs to be a paradigm shift in which eye care providers and rheumatologists become more familiar with the various ocular manifestations of SS. There is an urgent need for development of evidence-based screening algorithms for determining which patients with dry eye should be assessed for underlying SS to prevent delays in diagnosis. Existing SS disease activity measurement instruments need to be updated so that they effectively capture information about symptoms of visual dysfunction due to dry eye. Future research focused on the development of effective screening and treatment algorithms is needed to improve visual function and quality of life of patients.

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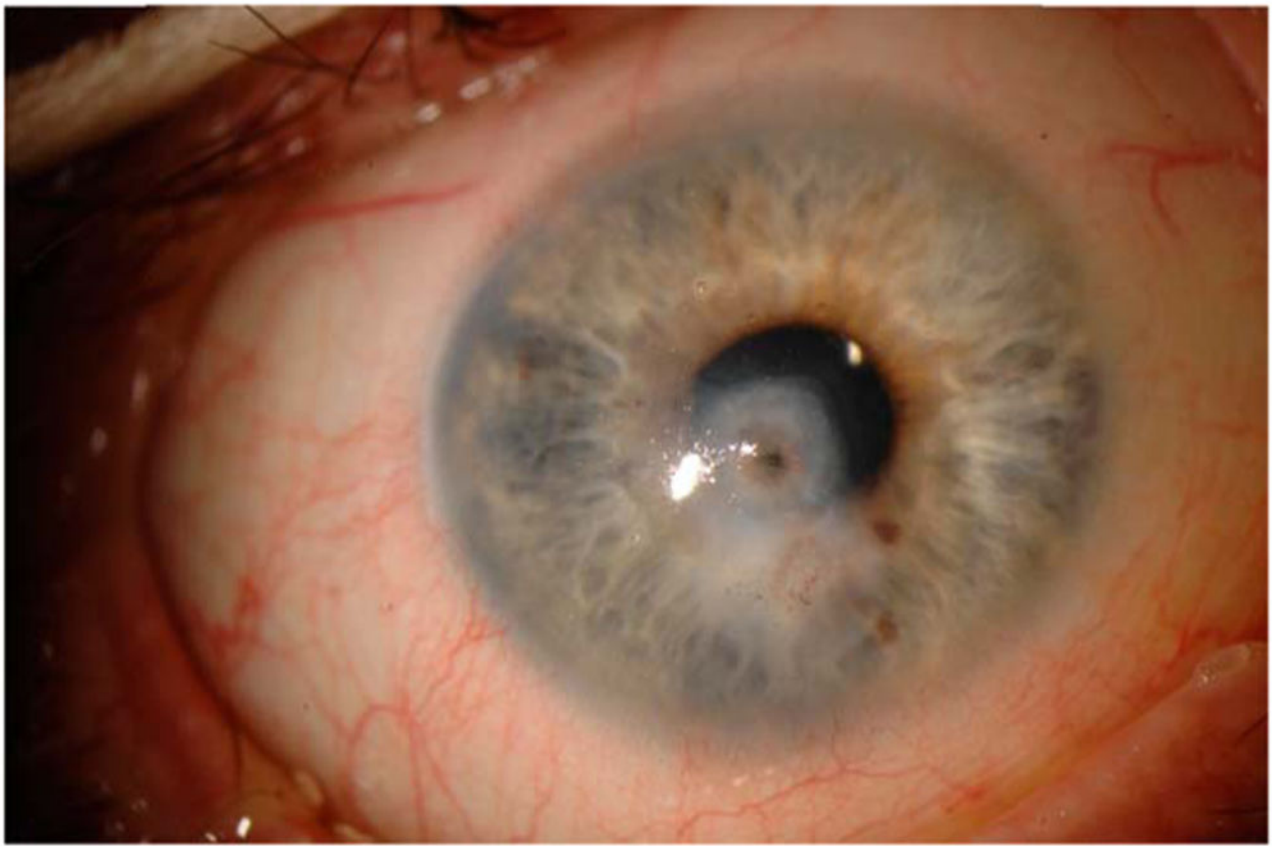

FIGURE 1.
Slit-lamp photograph of a patient with Sjögren syndrome who presented with sterile corneal melt and perforation.

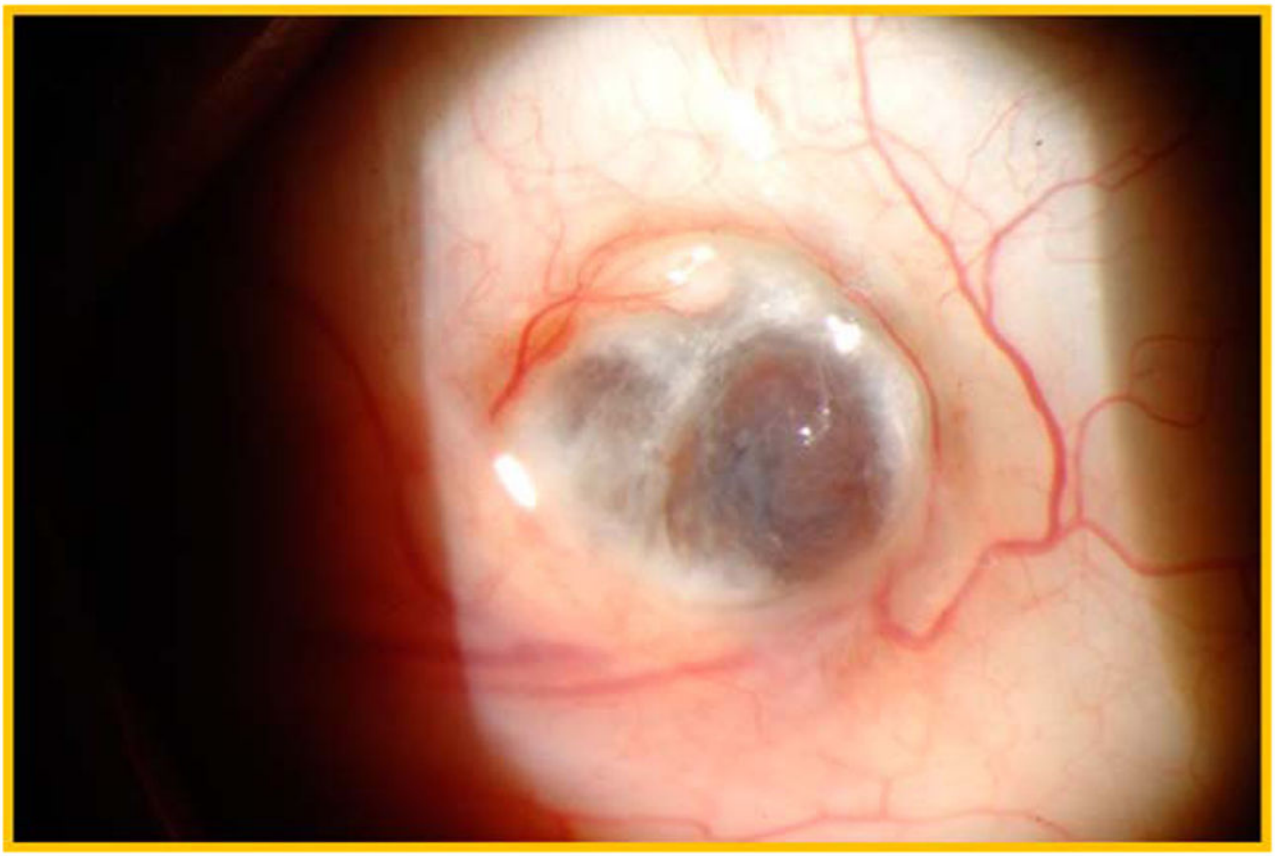

FIGURE 2.
Slit-lamp photograph of a patient with necrotizing scleritis due to primary Sjögren syndrome.

TABLE 1.

Extraglandular Ocular Complications of Sjögren Syndrome

Type of Complication	Cumulative Incidence (or No. Cases)	References	Study Design
Conjunctival inflammation			
Papillary conjunctivitis	1.4% of 163 patients	Akpek et al,[17] 2015	Cohort study
Follicular conjunctivitis	1.4% of 163 patients	Akpek et al,[17] 2015	Cohort study
Cicatrizing conjunctivitis	1.4% of 163 patients	Akpek et al,[17] 2015	Cohort study
Corneal inflammation			
Haze/scarring	1.4% of 163 patients	Akpek et al,[17] 2015	Cohort study
Sterile corneal ulcer/infiltration	0.7% of 163 patients	Akpek et al,[17] 2015	Cohort study
Corneal melt/perforation	1.4% of 163 patients	Akpek et al,[17] 2015	Cohort study
	5 cases	Gottsch,[29] 2000	Case series
	2 cases	Cohen,[28] 1982	Case series
	2 cases	Shan,[32] 2009	Case series
	1 case	Murtagh,[30] 2018	Case study
	1 case	Ou,[31] 2007	Case study
	1 case	Vivino,[33] 2001	Case study
Other inflammation			
Uveitis	2.0% of 163 patients	Akpek et al,[17] 2015	Cohort study
	8 cases	Rosenbaum,[35] 1987	Case series
	1 case	Bridges,[34] 1992	Case report
Scleritis/episcleritis	2.0% of 163 patients	Akpek et al,[17] 2015	Cohort study
	1 case	Ahmadi-Simab,[36] 2005	Case study
	1 case	Bamrolia,[37] 2012	Case study
	1 case	Choi,[38] 2012	Case study
Optic neuritis	2.0% of 163 patients	Akpek et al,[17] 2015	Cohort study
Retinal vasculitis	0.7% of 163 patients	Akpek et al,[17] 2015	Cohort study