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Research Article

The systematic review of Comorbidities with dry eye syndromes

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ABSTRACT

Dry eye or so called "keratoconjunctivitis siccais" is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface. The aim of this study was to overview coexistence of ocular diseases and dry eye syndrome. PubMed, Medline, Web of Science, and IranMedex databases were searched for eligible studies published from 1993 to 2016 to review comorbidities with dry eye syndromes. Based on the finding, coexistence of several diseases with dry eyes was diagnosed as following: dry eye macular degeneration, diabetes mellitus, LASIK, contact lens wear, Sarcoidosis, Sjögren's syndrome. Some studies indicated that dry eye disease is associated with many systemic diseases and some morbid conditions including dry eye macular degeneration, diabetes mellitus, LASIK, contact lens wear, Sarcoidosis, Sjögren's syndrome. The diagnosis of morbid condition would be helpful in selecting the type of treatment method allocated to each condition.

Key word: Comorbidities, Dry eye syndrome, Ophthalmology, Systemic disease

INTRODUCTION

Dry eyes are a frequent feature of routine ophthalmic clinical practice. The spectrum of dry eye disease ranges from mild tear film instability to severe dry eye which can threaten the integrity of the ocular surface and even lead to ocular perforation (1). Keratoconjunctivitis sicca decreased lacrimal gland secretion initiates ocular surface disease through a secondary increase in tear film osmolarity. Tear film osmolarity increases through a variety of mechanisms (2). It was shown that inflammation and the immune response play a major role in determining the health of the ocular surface in dry eye patients (3). Major risk factors for dry eye include age, female sex, certain medications and diseases, incisional refractive surgery, nutritional intake of essential fatty acids and disturbance in sex hormones due to a variety of causes (4).

The eye injury may be inflammatory, vascular or infectious, and iatrogenic (5). Eye diseases may affect different components of the eye (6). The ocular surface consist of eyelid margin, tear film, cornea, and conjunctiva (7).

Dry eye syndrome is characterized by symptoms,as ocular surface damage, reduced tear film stability, and tear hyperosmolarity. There are also inflammatory components (8).

Diseases of ocular surface are divided into two categories: 1) dry eye diseases; 2) non-dry eye diseases. Dry eye or so called "keratoconjunctivitis siccais" is a disorder of the tear film due to tear deficiency (9) or unstable tear film (10) accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (11). The tear film is consisted of three layers: the mucin, aqueous, and lipid layers. Dysfunction of each layers can result in dry eye disease (12).

There are two kinds of tear production, basic and reflex (13). Tears undergo four processes: production by the lacrimal gland, distribution by blinking, evaporation from the ocular surface and drainage through the nasolacrimal duct. Abnormalities (in any of) these steps can cause dry eye.

There are two major causes of dry eye syndrome: 1) aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE)(14). ADDE is primarily due to failure of lacrimal tear secretion, although failing in water secretion by the conjunctiva can also be a contributing cause (15). ADDE has two major subclasses, Sjögren Syndrome Dry Eye (SSDE) and nonSSDE (16).

In SSDE, autoimmune disease targeted the exocrine glands especially the lacrimal and salivary glands (14) . Sjögren's syndrome is a chronic inflammatory autoimmune disease that mainly affects the exocrine glands and usually presents as a persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. The histologic hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy) to a systemic process (17-20). Common ocular symptoms of Sjögren syndrome dry eye (SSDE) include burning, pruritus, photaesthesia, pain in the eyes, blurred vision, or tired eyes (21, 22) . In patients with SSDE, chronic ocular inflammatory lesions involve injury to the epithelial cells of the conjunctiva and cornea (23). As a result, ocular manifestations in SSDE are commonly more severe than in non-SSDE conditions(24, 25) .

There are two types of SSDE: Primary Sjögren Syndrome consists of systemic autoimmune disease in the absence of another discrete autoimmune disease (26, 27) .Secondary Sjögren Syndrome consists of primary Sjögren Syndrome features together with an overt autoimmune connective disease, most commonly rheumatoid arthritis (28, 29) . Non-SSDE is a form of ADDE due to lacrimal dysfunction, where systemic autoimmune features of SSDE have been excluded. It most commonly presents as age-related dry eye (ARDE), obstruction of the lacrimal glands, reflex hyposecretion due to sensory or motor block, and the use of systemic drugs (30).

The several factors are involved in suffering from this syndrome: Alcohol consumption(31), Smoking(32), low blink rates (eg, computer use), systemic and topical drugs, autoimmune diseases, contact lens wear, and cataract and refractive surgery(33), Sleep(34), Make up(35),Smartphone use(36), Depression and anxiety(37), Irritable bowel syndrome(38) ,sex hormone ((39)), (40), meibomian gland dysfunction(41) , short-term effect of air pollution (41), gout and hyperuricemia (42), visual display terminals (VDT) use(43), adiposity (44), and eye fatigue(45).

Dry eye diagnosis is done through clinical tests including vital dye staining, tear breakup time and Schirmer's test (46-48) ,symptom questionnaires, ocular surface staining, and osmometry(8).

It is important to determine clinically whether the dryness result from a local problem, or from a systematic disease process. Systemic problems may include autoimmune disorders (primary and secondary Sjögren’s syndrome), infiltrative disorders (such as lymphoma, Amyloidosis , hemochromatosis) and the process affect the

autonomic neural innervation of the gland (including medication side effects and disease such as multiple sclerosis)(49).

In this study, the comorbidity of dry eye with several morbid condition was discussed as dry eye macular degeneration, diabetes mellitus, LASIK, contact lens wear and Sarcoidosis.

Mechanism of action

Two interconnected mechanisms cause dry eye disease(DED): (1) dysfunction of lacrimal and meibomian glands, which leads to decreased tear production and/or an increase in tear evaporation; and **(2)** inflammation of the eye's surface triggered by internal immunopathological mechanisms, independent of tear deficiency and evaporation(50).

Degeneration of the retinal pigment epithelium (RPE) results in the death of photoreceptors, leading to loss of central vision (51)**.**

Meibomian gland dysfunction (MGD) is the most common cause of dry eye disease (DED). Eyelid inflammation, microbial growth, conjunctival inflammation, corneal damage, microbiological changes and DED result from tear film instability. The MGD results in increased melting temperature of meibum and subsequent meibomian gland blockage, reinforcing the vicious circle of MGD. Meibomian gland blockage, dropout and inflammation directly link the two vicious circles. MGD-associated tear film instability cause hyperosmolarity and inflammation, which are both the cause and consequence of DED (52).

Tear hyperosmolarity causes a decrease in tear volume, thinning of the aqueous tear film, and retarded spreading of the tear film lipid layer. This cause an increase in evaporative water loss and an added evaporative component to the dry eye. In The ADDE, Schirmer test score reduced with normal tear proteins of lacrimal origin(53). Hyposecretion of tears in dry eye may lead to pathologic changes in corneal epithelium and a decline in corneal sensitivity(54).

Mucins are among the many important constituents of a healthy tear film. Mucins secreted and/or associated with conjunctival goblet cells, ocular mucosal epithelial cells, and the lacrimal gland. They all must work together to create a stable tear film(55).

Inflammation is the core mechanism and plays a significant role in the pathogenesis of DED. Inflammation is a cellular response to factors that challenge the homeostasis of cells and tissues. Cell-associated and soluble pattern-recognition receptors, e.g. Toll-like receptors, inflammasome (?) receptors, and complement components initiate complex cellular cascades by recognizing or sensing various pathogens and damage-associated molecular patterns, respectively. Cytokines and chemokines represent alarm messages for leukocytes and once activated, these cells travel long distances to targeted inflamed tissues. Although it is a crucial survival mechanism, prolonged inflammation is damaging and participates in numerous chronic age-related diseases. It was indicated a crucial role of TSP-1(Thrombospondin-1) in maintaining the ocular immune and angiogenic privilege, for instance, by regulating T lymphocytes and the tolerance-promoting properties of ocular antigen-presenting cells(56).The chronicity of the disease suggests that dysregulation of immune mechanisms leads to a continues cycle of inflammation, accompanied by alterations in both innate and adaptive immune responses (57). Chronic dryness of the ocular surface results in inflammatory reactions and gradual destruction of the lacrimal glands and conjunctival epithelium. Once dry eye disease condition develops, inflammation is the key mechanism of ocular surface injury, as both the cause and consequence of cell damage (58).

Dry eye macular degeneration

One of the major causes of dry eye, meibomian gland dysfunction (MGD), shows increased prevalence with aging. MGD is caused by hyperkeratinization of the ductal epithelium of meibomian gland and reduced quantity and/or

quality of meibum, the holocrine product that stabilizes and prevents the evaporation of the tear film. It is important to note that retinoids which are used in current anti-aging cosmetics may promote the development of MGD and dry eye disease (59). it was shown that immunologic changes play a role in the pathogenesis of dry eye, not only in Sjögren's syndrome, but also in post infectious and age-related conditions(60). Orbital soft tissue involvement is more common in patients older than 50 years and in women. The anterior inferior quadrants of the orbits appear to be preferentially affected(61)

Quality of life in patients with dry age-related macular degeneration was compared in studied articles. The result showed that dry eye patients with similar visual acuity had similar overall impairment in Quality of life. beside, dry eye patients complained more about near and distance vision and dependency items(62).

The result demonstrated that The Age-Related Eye Disease Study 2 formulas did not cause progression of advanced AMD, compared to the original AREDS formula (63).

The sensitivity of blue-light fundus autofluorescence (FAF) and near-infrared autofluorescence (NI-AF) imaging was compared for determining the progression rates of macular lesions in dry age-related macular degeneration (AMD). Larger lesions showed higher progression rates than smaller ones in both imaging methods. Furthermore, NI-AF imaging is as important and effective as FAF imaging for follow-up of AMD patients with dry eye(64).

In dry eye, there is geographic atrophy with discrete areas of RPE loss whereas in the wet (exudative) form there is neovascularization penetrating from the choroid to retinal layers. Elevations in levels of local and systemic biomarkers indicate that chronic inflammation plays role in the pathogenesis of both disease forms (51).

Age-related dysregulation of innate and adaptive immune system responses was studied. Age-related changes in ocular surface immunity have similar and distinct characteristics to those changes seen in other mucosal tissues(65).

Diabetes mellitus

One of the mechanism responsible for dry eyes is autonomic dysfunction (66). Aldose reductase, the first enzyme of the sorbitol pathway, may also be involved (67, 68). Diabetic patients had with higher HbA1c values, lower values of tear secretion and lower values of tear break up time test (TBUT) (69). A more recent study showed that diabetes induced histological alterations in the lacrimal glands in mice. This finding also suggests that hyperglycemia-related oxidative stress may precipitate diabetic dry eye syndrome. the local inhibition of ACAT activity in tissue macrophages is protective against cholesteryl ester accumulation but causes cutaneous xanthomatosis in mice that lack apo E or LDLR (70).

In animal study, it was demonstrated that depressed corneal, cutaneous wound healing, dry eye, and abnormal corneal sensitivity in type 1 and type 2 diabetes can be reversed by OGF-OGFr blockade by NTX. Thus, the function of the Opioid Growth Regulatory System appears to be disordered in diabetic animals (71).

Poor glycemic control affects both the anterior and the posterior segments of the eye and increases prevalence of diabetes-associated DES (DMDES)(72).

The dry eye symptoms and signs was compared in both groups of diabetics and non-diabetics, and tear functions between diabetic subjects with and without dry eye. Dry eye symptoms were significantly associated with diabetics. Tear break up time was significantly shorter in diabetics with dry eye compared to diabetics without dry eye Muscle(73)

In an animal study, two common ocular inflammatory diseases, dry eye disease (DED), affect the ocular surface, and uveitis with inflammation of the inner eye .there are evidences suggest that certain T cell-targeting therapies can be used to treat both, dry eye disease and uveitis(74).

In patients with hemifacial spasm, magnetic resonance imaging (MRI) of the brain was done for any facial nerve compression or tumor involving posterior fossa. Botulinum type A injections were given after assessing their requirements on the basis of guidelines given (75).
In a study, it was shown that inflammation and the immune response play a major role in determining the health of the ocular surface in dry eye patients(3).
A study suggests that a subset of dry eye may be better represented as a chronic neuropathic pain disorder due to its features of dysesthesia, spontaneous pain, allodynia, and hyperalgesia (76).
The effect of autologous serum eye drops (ASED) on ocular symptoms, visual-related functioning and quality of life for patients failing other therapies was examined. ASED produce sustained benefits to dry eye symptoms, improve feelings of control and reduce requirements for assistance from others(77).
Several care methods showed strong scientific evidence to prevent dry eye, related to occlusion and ocular lubrication(78).
Several studies indicate a crucial role of TSP-1(Thrombospondin-1) in maintaining the ocular immune and angiogenic privilege, for example, by regulating T lymphocytes and the tolerance-promoting properties of ocular antigen-presenting cells(56).

LASIK

Dry eye is the most common complication after laser in situ keratomileusis (LASIK). The major cause of LASIK-associated dry eye is corneal nerve damage. LASIK has a neurotropic effect on the cornea, along with other changes in corneal shape that affect tear dynamics causing ocular surface desiccation. Preoperative dry eye condition is a major risk factor for more severe dry eye after surgery and should be identified prior to surgery(79).Eyes with femtosecond flaps had a lower incidence of LASIK-associated dry eye and required less treatment for the disorder (80).The magnitude of the preoperative tear volume (inferred from clinical testing) may affect the recovery of the ocular surface after LASIK such that a large tear volume decreases the likelihood of chronic dry eye after LASIK (80). Chronic dry eye was uncommon after PRK and LASIK (81).
Experience with Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) treatment for complications after laser in situ keratomileuisis (LASIK) was reported. PROSE treatment is an effective option for management of ectasia, cornea first surface aberrations, dry eye, and corneal neuralgia after LASIK, even in patients who are contact lens intolerant(82).
Postoperative ocular surface integrity, innervation between small incision lenticule extraction (SMILE) and femtosecond laser-assisted laser in situ keratomileusis (FS-LASIK) was compared. The SMILE procedure has fewer negative impacts on the ocular surface and corneal innervation than does FS-LASIK. Furthermore, SMILE is more preferred than FS-LASIK by exhibiting a lower risk of postoperative dry eye(83).
It was determined whether patients without preoperative dry eye have an altered conjunctival goblet cell density and mucin secretion postoperatively. Patients without apparent dry eye had an altered conjunctival goblet cell population after PRK or LASIK. The conjunctival goblet cell population tended to decrease in the early postoperative period after either surgery and was most depended on preoperative goblet cell density. The changes in the tear film and ocular surface did not seem to affect goblet cell mucin secretion after either procedure (84).
The associations between dry eye, corneal nerves, and tear neuroptides in dry eye after LASIK was investigated. The results showed the association between tear neuropeptides, conjunctival sensitivity, and symptoms in symptomatic patients after LASIK. The differences in nerve morphology, neuropeptide, and ocular surface sensitivity between symptomatic and

asymptomatic patients after LASIK are required to understand better the mechanism of dry eye after LASIK(85).

Small incision lenticule extraction (SMILE) with femtosecond laser-assisted in situ keratomileusis (FS-LASIK) for treating myopia was compared. The results showed both FS-LASIK and SMILE are safe, effective and predictable surgical options for treating myopia. However, dry eye symptoms and loss of corneal sensitivity may occur less frequently after SMILE than after FS-LASIK(86).

The prevalence and severity of dry-eye disease in patients with myopia being evaluated for laser in situ keratomileusis were assessed. Dry-eye severity was predominantly mild/episodic. The proportion of patients requiring dry-eye therapy (based on OSDI and DEWS severity findings) was almost 2 times higher than the proportion receiving treatment.

Dry-eye manifestations after photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) were evaluated and the incidence and predictive factors of chronic dry eye using a set of dry-eye criteria were determined. Chronic dry eye was uncommon after PRK and LASIK. Ocular surface and tear-film characteristics during pre-operative examination might help to predict chronic dry-eye development in PRK and LASIK (81).

The performance of a point-of-care test for detection of matrix metalloproteinase 9 (MMP-9) levels in post-laser-assisted in situ keratomileusis (LASIK) dry eyes was evaluated. Only half of post-LASIK dry eyes were found to have significant inflammation associated with elevated MMP-9. The OSDI is useful to non-specifically identify patients with symptomatic dry eye while the Inflammatory determined which patients with dry eye were associated with significant inflammation that may guide therapeutic management decisions(87).

Dry eye disease following SMILE versus FS-LASIK. SMILE produces less dry eye disease than FS-LASIK at 6 months postoperatively but demonstrates similar degrees of dry eye disease at 12 months(88).

The regeneration of subbasal epithelial nerve plexus in the central cornea and dry eye condition between patients undergoing conventional LASIK surgery and femtosecond-assisted LASIK surgery was compared. The difference between conventional LASIK and femtosecond-assisted LASIK does not significantly affect the dry eye test values and nerve fiber measurements in patients at 1 year after LASIK(89).

Changes in nerve morphology, tear neuropeptide, and dry eye was evaluated and the relationship between reinnervation and dry eye and to assess the role of tear neuropeptides in reinnervation post-LASIK. An inverse relationship between reinnervation post-LASIK and dry eye symptoms was found, confirming that post-LASIK dry eye is a neuropathic disease. It was demonstrated an association between tear SP and post-LASIK reinnervation, suggesting strategies for manipulating neuropeptide concentration to improve reinnervation may lead to ocular comfort post-LASIK (90).

The changes in intraocular scattering before and after instillation of rebamipide ophthalmic suspension in patients with dry eye after corneal refractive surgery was assessed. Rebamipide ophthalmic suspension was effective for improving both ocular surface parameters and optical quality in patients with dry eye undergoing corneal refractive surgery, suggesting that it may hold promise for the treatment of such patients (91).

It is now increasingly understood that corneal nerve damage produced by LASIK surgery resembles the pathologic neuroplasticity, associated with other forms of persistent post-operative pain, which may underlie certain persistent dry eye symptoms after LASIK surgery (92).

visual outcome and higher order aberrations (HOA) between wavefront-guided LASIK(WF-

LASIK) and wavefront guided PRK (WF-PRK) was compared in patients with high preoperative HOA.WF-LASIK and WF-PRK have similar efficacy, safety and predictability, though WF-PRK induces less HOA(93).

Small incision lenticule extraction (SMILE) versus LASIK for post-refractive dry eye disease was compared. The SMILE procedure has a less pronounced impact on the ocular surface and corneal innervation compared with LASIK, further reducing the incidence of dry eye disease and subsequent degradation in quality of life after refractive surgery (94).

Corneal sensation and self-reported dry eye symptoms after femtosecond-assisted LASIK with conventional versus inverted side cuts was compared. The LASIK flaps with an inverted side cut are associated with superior recovery of corneal sensation compared with flaps with a conventional side cut during the first postoperative year; however, this may not translate to significant improvements in subjective dry eye symptoms(95).

Contact lens

eye normal function depends on the interrelationship of its lipid, aqueous, and mucin components, which are spread by the lids over an intact corneal epithelium. Alterations in the tear film frequently produce clinical symptoms and signs. Contact lens wear has been associated with changes in tear composition(96). Disturbances of the quantity or quality of the tear film, whether because of aqueous deficiency or evaporative tear problems, results in intolerance of contact lens wear and damage to the ocular surface(97). Contact lens wearers were divided into two groups: with and without dry eye symptoms. Contact lens wearers with dry eye symptoms had decreased mucin concentrations at the ocular surface, and that more of their mucin were contained in macromolecular aggregates. Symptomatic soft contact lens wearers exhibit significantly more severe Lid wiper epitheliopathy(LWE) and lid parallel conjunctional folds (LIPCOF), while ocular surface mucin composition is conserved(98). Besides, the scleral contact lenses are extremely well accepted by keratoconic patients because of comfort and vision these devices provide. For many patients, they offer further relief from dryness symptoms. However, midday fogging remains a limitation for many wearers(99).

The prevalence of soft contact lens-related (SCL) dryness symptoms in large populations of SCL wearers in North America (NAm) and the United Kingdom (UK) was compared. SCL wearers in NAm reported longer hours of wear with significantly more symptoms of dryness and discomfort. NAm wearers used dryness treatments more often, but experienced less relief than UK wearers. In both regions, the CL-DE categorization was useful to predict poorer comfort, shorter comfortable wearing time, and increased use of treatments(100).

Longitudinal changes in Langerhans cell density (LCD) in the human cornea and conjunctiva during asymptomatic and symptomatic contact lens wear was determined. The initial transient increase in corneal and conjunctival LCD in CLIDE (versus NO-CLIDE) suggests an inflammatory component in the aetiology of this condition(101).

The behavior of prelens tear film (PLTF) and postlens tear film (PoLTF) after the instillation of diquafosol was investigated using contact lens. Instillation of 3% diquafosol ophthalmic solution increases PLTF and PoLTF in rabbit eyes with contact lenses. Diquafosol is effective as a treatment option for contact lens-related dry eye(102).

Comfort and related experiences of adapted keratoconic scleral contact lens (17-18.2 mm) wearers were assessed. The results showed that the scleral contact lenses are extremely well accepted by keratoconic patients due to providing of comfort and vision. For many patients, they offer further relief from dryness symptoms. However, midday fogging remains a limitation for many wearers (99).

The signs and symptoms of dry eye and dinucleotide secretion in tears of keratoconus patients (KC) and the potential effect of rigid gas permeable (RGP) contact lens wear were evaluated. The finding was indicated that factors such as RGP contact lens wear might exacerbate the clinical condition of dry eye (103).

Patient satisfaction and perceived outcomes with different methods of refractive error correction were assessed. Compared with contact lens wear, current LASIK technology improved ease of night driving, did not significantly increase dry eye symptoms, and resulted in higher levels of satisfaction at 1, 2, and 3 years follow-up (104).

A case of refractory dry eye management with semi-scleral contact lens was described. Dry eye was associated with facial nerve (cranial nerve VII) palsy as a result of cerebellopontine angle tumor surgery. Her ophthalmic examination revealed scleral exposure because of lagophthalmos, conjunctival hyperemia, corneal debris, scar, and diffuse punctate epitheliopathy on her right eye. Lissamine green staining showed diffuse conjunctival and corneal staining. (105).

Results of the 8-item Contact Lens Dry Eye Questionnaire (CLDEQ-8) among a large sample of SCL wearers before and during 1 year after fitting with one of 2 daily disposable (DD) lenses (etafilcon A or narafilcon B) in the TEMPO Registry were reported. Use of the CLDEQ-8 in clinical practice and clinical research will help quantify and standardize symptom measures in SCL wearers (106).

The efficacy of topical application of 3% diquafosol tetrasodium solution for the treatment of soft contact lens (SCL) wearers with dryness was evaluated. Topical application of diquafosol solution to the SCL wearers with dryness improved biomarker of membrane-associated mucins, BUT, staining of cornea and conjunctiva, and subjective symptoms (107).

Microstructural alterations of corneal and limbal epithelial cells in healthy human corneas and in other ocular conditions were analyzed. The result demonstrated morphological differences in the basal and intermediate epithelium between limbus and central cornea, and found no difference between contact lenswearers, dry eyes, and normal subjects (108).

The relationship between tear menisci and corneal subbasal nerve density (SND) in long-term soft contact lens (CL) wearers investigated. Soft CL wearers with dry eye symptoms have reduced tear menisci. The alteration of midperipheral corneal SND may contribute to dry eye symptoms (109).

It was determined whether Langerhans cells in the lid wiper are upregulated in contact lens-induced dry eye (CLIDE). Results illustrated that Langerhans cells in the lid wiper are upregulated in CLIDE, suggesting an inflammatory component in the etiology of this condition(110).

It was hypothesized that wearing contact lenses is associated with changes in the ocular microbiota. The results indicate that wearing contact lenses alters the microbial structure of the ocular conjunctiva, making it more similar to that of the skin microbiota(111).

Discomfort and dryness symptoms at the end of the day are lower in the OK CL group than in the Si-Hy CL group(112).

Sarcoidosis

Sarcoidosis is a multisystem disease with unknown cause that is characterized histologically by the presence of noncaseating epithelioid cell granulomas in multiple organs (lymph nodes, lungs, spleen, liver, skin, and salivary and lacrimal glands). The diagnosis is established when clinical and radiologic findings are supported by histologic evidence of noncaseating granulomas. Sarcoidosis shares several of the extraglandular features of SS, as well as the involvement of the salivary and lacrimal glands, making it difficult to differentiate between the 2 diseases on clinical grounds alone (113).

Ocular inflammation from sarcoidosis may involve the eye, the tissue around the eye lacrimal system, and the orbit (61). Multiple parts of the eye may be involved simultaneously. The following regional areas characterize the

important aspects of sarcoidosis-associated ocular inflammation. Uveitis is the most common ocular manifestation of sarcoidosis, and it is potentially visually threatening (114).

Clinical similarities and disparities in the course of sarcoidosis and systemic connective tissue diseases, particularly Sjögren's syndrome, have been evaluated. It has been highlighted that all the organs can be involved in sarcoidosis. Prompt diagnosis and a proper therapeutic approach are of vital importance (115).

the biomarkers associated with Sjögren's syndrome (SS) identified in the serological samples of patients with refractive dry eye disease was assessed; Evaluation for salivary protein-1, parotid secretory protein 1, and carbonic anhydrase VI biomarkers allows identification patients subset with biomarkers associated with SS that may not be identified through the traditional assessments (SS-A/SS-B)(116).

Recently, newer biomarkers have been identified, including autoantibodies to salivary gland protein-1, parotid secretory protein, and carbonic anhydrase VI, and may allow for earlier diagnosis of SS (117).

The possibility of using salivary electrophoresis to differentiate between the Sarcoidosis and Sjögren's syndrome diseases was investigated. No difference was observed in salivary flow rate, total salivary protein, or electrophoretic profile between patients with sarcoidosis and patients with Sjögren's syndrome. Salivary protein electrophoresis does not appear to be useful to differentiate between sarcoidosis and Sjögren's syndrome (118).

A 53-year-old man, who had received salvage chemotherapy for follicular lymphoma, complained of fever and dry cough. High-resolution computed tomography of the chest showed bilateral diffuse ground-glass opacities with weak F18-fluorodeoxyglucose uptake on positron emission tomography. Transbronchial lung biopsy specimens revealed noncaseating epithelioid cell granulomas. Sarcoidosis was diagnosed (119).

Sjögren syndrome

Dry eye syndrome is the most common ophthalmic manifestation of rheumatoid arthritis. Dry Eye affect those with Sjögren's syndrome, rheumatoid arthritis, and scleroderma (120).

the lacrimal gland (LG) is the primary source of aqueous tears containing diverse proteins that protect and sustain the ocular surface (29).

Primary Sjögren's syndrome (pSS) is a systematic autoimmune disease characterized by high lymphocytic infiltration in the exocrine glands such as salivary and lacrimal gland (121). Dryness, pain and fatigue are the most clear symptoms of pSS, and they affect patients quite much (122) .

A case of miliary sarcoidosis with secondary Sjogren's in a 45-year-old male who presented with symptoms of sicca syndrome in the form of dryness of eyes and mouth with parotid swelling was reported. Computed tomography of thorax showed mediastinal and hilar lymphadenopathy, bilateral miliary opacities in lung parenchyma. Whole body FDG PET/CT showed involvement of both parotids, liver, diffuse uptake in lungs, mediastinal and retroperitoneal lymph nodes (123).

Light backscattering (LB) in corneal layers in patients with primary Sjögren's syndrome dry eye (SSDE) was evaluated and the eventual association with the lacrimal functional test values was determined. A perfect reverse correlation between the light reflectivity measures at BM with Schirmer test with ($r = -0.91$) and without ($r = -0.90$) stimulation and BUT ($r = -0.88$) was found (124).

A 44-year-old female diagnosed with histologically proven coexistence of primary Sjögren's syndrome and sarcoidosis with pulmonary and muscular involvement was reported. The differential diagnosis may be difficult, but this is not an exceptional case, which highlights the need to critically revise the consideration of sarcoidosis as an exclusion for primary Sjögren's syndrome, as established in current classification criteria (125).

In an animal study, the male NOD mouse as a model for SS-associated dry eye was used. In addition to developing lymphocytic infiltration in the LG, the result has revealed upregulation of several mediators of inflammation in the diseased LG, including cytokines, such as IL-10, IL-12a, and IFN-γ, and lysosomal cysteine proteases, like Cathepsin S (CTSS) and Cathepsin H(126). Furthermore, it was shown increased activity of CTSS not only in the LG of male NOD mice but also in their tears. This finding confirmed elevated tear CTSS in SS patients(127), suggesting CTSS as a tear biomarker of SS-associated dry eye.

Amyloidosis

Amyloidosis is a condition in which an abnormal protein called amyloid builds up in tissues and organs. Amyloidosis is a serious health problem that can lead to life-threatening organ failure. The type of protein and where it collects determines the type of amyloidosis. Amyloid deposits may collect throughout body or in just one area (49, 128-131).

There are different types of amyloidosis, including: 1) Primary (systemic AL) amyloidosis, 2) Secondary (systemic AA) amyloidosis, 3) Dialysis-related amyloidosis (DRA), 4) Familial, or hereditary, amyloidosis (AF), 5) Senile systemic amyloidosis (SSA), 6) Organ-specific amyloidosis (132, 133).

Secondary (systemic AA) amyloidosis: This is the result of a chronic inflammatory disease, such as lupus, rheumatoid

arthritis, tuberculosis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and certain cancers . The amyloid type A protein (AA) causes dry eye type of amyloidosis (134).

A patient had severe sicca complex. Histopathologic and immunologic examination of the salivary glands showed amyloid fibril infiltration, type A lambda VI. To our knowledge, this is the first documentation of immunologically characterized primary amyloidosis causing the sicca complex. The sicca complex is usually associated with Sjögren's syndrome and the presence of autoantibodies to SSA and SSB. These antibodies were absent in our patient, despite the severity of the sicca syndrome. The clinician should consider more unusual causes of the sicca complex, eg, amyloidosis, particularly if the serologic markers of antibodies to SSA and SSB are absent. Tissue typing the amyloid protein diagnosed primary amyloidosis, obviating the need to search for underlying disease (135).

Sicca syndrome (SS), consisting of xerostomia and xerophthalmia, may be caused by various disease processes. We present a unique case of SS secondary to primary amyloidosis. Amyloidosis is a rare but definite cause of SS and should be included in the differential diagnosis of any patient who presents with sicca symptoms. A literature review compared amyloidotic patients with SS and without SS. it demonstrated both of these groups present similar regardless to symptoms. However, the majority of patients with SS present with sicca symptoms initially in addition to symptoms of amyloidosis. These SS patients can also present with proteinuria and negative serology test results. Therefore, patients presenting with sicca symptoms, proteinuria, and negative serologic findings should be suspect for amyloidosis. The importance of distinguishing the diagnosis of Sjögren's syndrome from SS in these patients cannot be overemphasized. There is a significantly higher incidence of developing a lymphoma in Sjögren's syndrome patients. This has important implications for the head and neck surgeon treating these patients (136).

Vesical bleeding and sicca complex proved to be due to unrecognized amyloidosis in a patient with chronic rheumatoid arthritis. The features of amyloidosis of the lower genitourinary tract are outlined (137).

Sicca syndrome consists of two major clinical findings: keratoconjunctivitis sicca and xerostomia due to destruction of the lacrimal and salivary gland parenchyma. Although it is most often due to Sjögren's syndrome, a variety of other diseases causes sicca syndrome. The rare case of a patient with gland infiltration in primary amyloidosis was reported. Sonographic, computed tomographic and magnetic resonance findings are presented (138).

CONCLUSION

Some studies indicated that dry eye disease is associated with many systemic diseases and some morbid conditions including dry eye macular degeneration, diabetes mellitus, LASIK, contact lens wear, Sarcoidosis, Sjögren's syndrome. The diagnosis of morbid condition would be helpful in selecting the type of treatment method allocated to each condition. More importantly, inflammation and immune response play a major role in determining the health of the ocular surface in dry eye patients. Therefore, the drugs that affect these parameters especially the plants based remedies might be beneficial (139-141). Ocular diseases are also associated with oxidative stress. Hence, the antioxidants, particularly herbal medicines with antioxidant activity (142-146) might be effective.

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