Corneal Findings in Rheumatologic Diseases

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Received 15 March 2014; Published online 26 April 2014

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Abstract

Cornea is a major structure of eyes affected in rheumatologic patients. It is important to know corneal findings in rheumatic diseases because it can provide early diagnosis and treatment for systemic disease and reduce the risk of complications as irreversible visual loss. In this article, we will summarize and discuss the corneal findings and the formation mechanisms in the diseases of Sjogren's syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis.

Keywords: Rheumatologic diseases; cornea; Sjogren's syndrome; rheumatoid arthritis; juvenile rheumatoid arthritis; ankylosing spondylitis

1. Introduction

Rheumatic conditions affect a wide variety of tissues and often associated with ophthalmic findings (Petris and Almon, 2012). The inflammation in rheumatologic diseases can affect all structures of the eye and often occurs as iridocyclitis, vitritis, keratitis, scleritis and retinal vasculitis (Coskun and Alkan, 2009). Cornea is one of the major structures of the eye affected in rheumatologic patients (Patel and Lundy, 2002).

The cornea may be affected in various ways. Corneal signs and symptoms of dry eye accompanying rheumatic diseases may occur, in some cases, corneal thinning, corneal ulcers and even corneal perforation can occur (Patel and Lundy, 2002). Knowing that the corneal findings in rheumatic diseases are important, as it can provide early diagnosis and treatment for systemic disease and reduce the risk of complications as irreversible visual loss (Lightman and Taylor, 2011). Findings may be associated with the disease itself or with the systemic immunosuppressives used in therapy (Coskun and Alkan, 2009). Pain, itching, tearing, burning, stinging, redness and loss of vision are among the corneal symptoms that may be observed in cases of various rheumatic diseases (Petris and Almony, 2012) (Table 1, Table 2).

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Sjogren’s syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis are rheumatologic disorders accompanied by ocular inflammation and affected cornea relatively more frequently (Patel and Lundy, 2002). In this article, we will focus on the corneal findings and the formation mechanisms in these diseases.

### Table 1 The most ocular manifestations in rheumatologic disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ocular Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Keratoconjunctivitis sicca, keratitis, ulcerative keratitis, corneal perforation, scleritis, episcleritis, choroiditis, retinal vasculitis, episcleral nodules, retinal detachments, macular edema</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Keratoconjunctivitis sicca, corneal melting, corneal perforation</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>Uveitis, dry eye, band keratopathy</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Uveitis, superficial keratitis, corneal ulcers</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Keratoconjunctivitis sicca, stromal keratitis, conjunctivitis, uveitis, episcleritis, scleritis, retinal vasculitis, proliferative retinopathy, optic neuritis, hemianopia, amaurosis, internuclear ophthalmoplegia, pupillary abnormalities</td>
</tr>
</tbody>
</table>

### 2. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune connective tissue disease. Rheumatoid factor (RF) is a kind of antibody that binds to IgG and responsible for the inflammation (Zlatanovic at al., 2010). Ocular manifestations involved with RA are keratoconjunctivitis sicca, episcleritis, scleritis, corneal changes and retinal vasculitis. Keratoconjunctivitis sicca is the most common of these findings (CCS), the prevalence is approximately 90% (Villani at al., 2008). 11% to 33% of RA patients have secondary Sjogren’s syndrome. CCS is seen more often and in milder forms in this association (Senel at al., 1995).

Keratoconjunctivitis sicca occurs due to aqueous deficiency. Direct damage to the lacrimal gland, gland atrophy or neurosecretory block cause aqueous tear deficiency (Petris and Alon, 2012). Patients’ complaints are dryness, foreign body sensation, photophobia, decreased vision and pain.

Schirmer’s test with or without anesthetic is used to evaluate aqueous tear production and tear breakup time (tBUT) test is used to measure tear film stability. Abnormal keratinized cells in epithelial ocular surface are painted with Fluorescein 1% eyedrop in corneal area and rose bengal 1% eyedrop in conjunctiva and this method is used in the diagnosis of dry eye.
Table 2 Ocular Signs and Symptoms in Rheumatologic Disease

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis, corneal ulceration</td>
<td>Pain with photophobia, foreign body sensation, tearing, red eye, decreased vision</td>
<td>Inflammatory cell infiltrate, corneal opacification, corneal vascularization, corneal ulceration, perforation</td>
<td>NSAIDs, topical/oral/IV steroids, Immunomodulators, Surgery (ulcer debridement, conjunctival resection, corneal graft, application of tissue adhesives)</td>
</tr>
<tr>
<td>Keratoconjunctivitis sicca</td>
<td>Dry eye, burning, pain, blurred vision, pruritus, foreign-body sensation, mucous threads and crusting about the eyelids</td>
<td>Diminished corneal tear meniscus, abnormal Schirmer's test</td>
<td>Sunglasses, Tear substitutes, cyclosporine, immunomodulator, autolog serum, surgery (punctal occlusion and lateral tarsorrhaphy)</td>
</tr>
</tbody>
</table>

These patients should use topical lubricants throughout their life. The use of chronic topical drops changes the flora and causes the growth of antibiotic-resistant microorganisms (Zlatanovic et al., 2010). Therefore cyclosporine A 0.05% (Restasis), modifying agents like anti-TNF (infliximab) or autologous serum are used in conjunction with artificial tears. Warm compresses and eyelid scrubs are used to support the lipid layer of tears. If these treatments fail, punctal occlusion and lateral tarsorrhaphy may be considered (Petris and Alon, 2012). Patients should be informed about using sunglasses, room humidifiers and avoiding dry environments (Patel and Lundy, 2002).

A study performed by using fluorescein and rose bengal dye for showing abnormal keratinized cells in epithelial ocular surface method by Lee et al. showed that keratinized cells are more common in the upper cornea. This is because the superior cornea has intense vascularization, and consequently intense cytokin exposure (Lee et al., 2012). In addition, the superior cornea is in contact with the upper palpebral conjunctiva; therefore it may be more exposed to the inflammatory cytokines expressed from the palpebral vasculature. According to these results they report that the increase in cytokines is more harmful to epithelial cells than aqueous tear deficiency (Lee et al., 2012). In the same study, it was reported that symptoms and severity of clinical findings increase with age (Lee et al., 2012).

In a study conducted by using Scheimpflug imaging system, corneal thickness and corneal volume of the patients with rheumatoid arthritis were found to be significantly lower than those of the control group (Cingu et al., 2013). However, duration of disease does not affect the pachymetric measurement or corneal volume. These measurements were the lowest in RA patients with dry eye. In the cases of RA patients, metalloproteinase enzyme activity increases and it is thought to be the cause of these changes. Metalloproteinases are released from Langerhans islet cell, a kind of a dendritic cell. They shred type 4 collagen, which causes corneal
thinning (Cingü et al., 2013). Also it is reported that intensive topical corticosteroids used in the treatment of scleritis may also cause corneal thinning (Senel et al., 1995).

In a study researching corneal biomechanical changes in rheumatoid arthritis patients by using ocular response analyzer, it has been observed there is no significant difference between rheumatoid arthritis patients and the healthy population regarding cornea fixed intraocular pressure, Goldman compatible intraocular pressure, corneal hysteresis and corneal resistance factor (Altınkaynak et al., 2011).

In many studies carried out on patients with RA, OSDI scores (ocular surface disease index) were high but Schirmer's test score, tBUT score and corneal sensitivity were lower (Villani et al., 2008; Kim et al., 2012). In a study performed on patients with RA by using confocal microscopy, in spite of cell densities in surface epithelium was significantly low, cell densities in basal epithelium and stroma were significantly high. The number of active keratocytes (hyperreflective stroma) was higher in RA patients. The reason was stated to be increased metabolic activity depending on increased inflammation (Villani et al., 2008). In the same study on RA patients, it has been shown that the nerve number in plexus subbasal was less, beadlike formation and tortuosity were high (Villani et al., 2008). The other corneal involvement observed in patients with RA is peripheral ulcerative keratitis (Fig. 1) (Patel and Lundy, 2002; Petris and Almon, 2012). It is thought to be caused by cytokines and collagenases released after inflammation (Lightman and Taylor, 2011). Topical and oral steroids, topical antibiotics, immunomodulators such as rituximab, metalloproteinase inhibitors, and topical medroxyprogesterone acetate are used for treatment (Petris and Almon, 2012). Serious complications like corneal perforation (Fig. 2) may occur in untreated corneal ulcer patients and surgical treatment like ulcer debridement, conjunctival resection, corneal graft, application of tissue adhesives, sclerectomy, and scleral patch grafting may be necessary (Freissler and Lang, 1996; Patel and Lundy, 2002).

Cogan’s syndrome which presented with interstitial keratitis and hearing loss may be associated with RA (Lee et al., 2012). It has been reported that corneal melting and necrotizing scleritis can occur in RA patients after cataract surgery. These findings were helpful to diagnose previously undiagnosed RA patients (Perez et al., 2002). Jones and Maguire studied 70 patients with RA who underwent cataract surgery. Three patients developed diffuse superficial punctate keratopathy but they had a preoperative history of keratoconjunctivitis sicca. There aren't too many corneal complications after cataract surgery in patients with rheumatoid arthritis (Jones and Maguire, 1992).

### 3. Sjogren's Syndrome

Sjogren's syndrome (SS) is a chronic and systemic autoimmune disease that occurs as a result of salivary and lacrimal gland infiltration with lymphocytes and plasma cells. Responsible antibodies are anti SS-A (Ro), SS-B (La), fodrin, alpha-amylase, anti carbonic anhydrase. It's characterized by mouth and eye dryness (Nguyen and Peck, 2009). In primary Sjögren's Syndrome autoantibodies are only against the lachrymal and salivary glands, however secondary Sjogren's syndrome is associated with rheumatoid arthritis or other rheumatic diseases such as SLE (Nguyen and Peck, 2009). CCS is the most common manifestation observed on patients with SS. It has been shown that infiltration is not the only reason behind tear deficiency. However, epithelial morphology changes, release of inflammatory mediators and
immune reactions by agents of histocompatibility (HLA-DR) play a role in the development of CCS (Villani at al, 2007).

Schirmer’s test, tear breakup time (tBUT) test, fluorescein and rose bengal dye are used in the diagnosis of dry eye (Fig. 3). John P et al. have updated the classification of CCS by using tBUT, Schirmer, conjunctival staining with rose bengal and corneal staining with fluorescein in 2010. They found that all the scores in SS with CCS were higher than the only CCS (Whitcher at al, 2010).

![Peripheral corneal thinning in patient with Rheumatoid Arthritis.](image)

**Fig. 1.** Peripheral corneal thinning in patient with Rheumatoid Arthritis.
Peripheral corneal thinning, corneal ulcer and corneal perforation in patient with Rheumatoid Arthritis.

Villani et al. analyzed corneal thickness, epithelium and stroma density and subbasal plexus with confocal microscopy in patients with primary and secondary Sjogren’s syndrome. They found that the corneal thickness was thinner in primary and secondary Sjogren’s syndrome compared to the control group. This result may depend on the proteolysis and apoptosis caused by markers of inflammation such as TNF and IL. In patients with Sjogren’s syndrome, superficial epithelial cell density and stromal density were higher. While corneal surface damage reduces the epithelium density, stromal activated keratocytes lead to an increase in stromal density. Furthermore, the number of nerves in the subbasal plexus was lower in Sjogren’s syndrome. They suggested that existing corneal hypoesthesia in SS occurred due to this reason. Increasing nerve growth factors are described to be responsible for the increased tortuosity (Villani at al, 2007).

Patel and McGhee have reached similar conclusions in another study performed by using in vivo confocal microscopy. They thought that the decreased number of nerves in Subbasal plexus was related to the fact that the corneal innervation and the production of aqueous tear are affected by cranial and peripheral neuropathy which can occur in Sjogren's syndrome. And the reduced number of nerves in the subbasal plexus may cause corneal hypoesthesia (Patel and McGhee, 2009).
In a study, it has been observed that the reason for the reduction of corneal sensitivity is ocular surface disorder due to lack of tears. Physiological adaptation to irritation symptoms develops resulting in surface defects; the pain threshold increases and higher dose stimulus is required to induce the cornea. This deterioration of protective mechanisms is considered a threat for possible infections (Iskeleli et al., 2001).

The assay results revealed Sjogren’s syndrome in 2 patients who underwent Descemet’s stripping endothelial keratoplasty (DSEK) and presented with sterile corneal melting and wide epithelial defects. Current tear failure, the topical drops, traumas to cornea during surgery increase epithelial damage and prevent healing. The fact that corneal melting occurs even by surgical techniques applied without touching epithelium, such as DSEK revealed the need to exclude underlying collagen connective tissue disease before corneal surgery (Shannon et al., 2009).

In a study, two patients with SS had CCS and vision loss after corneal perforation was observed to have high levels of the metallopreteinase enzyme in cornea. This complication could be prevented by the use of metallopreteinase enzyme inhibitors (Brejchova et al., 2009). It has been shown that wearing contact lenses well tolerated in SS. A female contact lens wearer was diagnosed with SS and used hydroxypropyl cellulose ophthalmic drops once-daily for more than 25 years and there were no significant side effects or changes in visual acuity (Wander AH. 2011). Similarly in a study, there were no associations between dry eye severity and contact lens wear. It may be due to the avoidance of contact lens wear in cases with severe dry eye (Lee et al., 2012).

### 4. Juvenile idiopathic (Rheumatoid) Arthritis

Juvenile rheumatoid arthritis (JRA) is the general name characterized by at least one joint involvement for more than six weeks in children under the age of 16. The most ocular finding is iridocyclitis and approximately 80 percent of cases of uveitis in children have JRA, most commonly pauci-articular subtype (Akıncı et al., 2007). The prevalence of dry eye is assumed to be about 5% in juvenile rheumatic diseases. Especially during the active period and after long years, severe dry eye cases may occur. During periods of active disease and long-term illness, tBUT and Schirmer values are lower (El-Shazly adn Mohamed, 2012). Similarly Akıncı et al. have reported that basal tear secretion and tear film stability was lower, men and patients with long-term disease had higher risk in JRA patients (Akıncı et al., 2007).

In some children with JRA, there is not so much symptom in uveitis and eye is calm. In these children, it’s diagnosed after occurrence of corneal findings. One of these corneal findings is band keratopathy. Band keratopathy has been reported as another corneal complication in children with JRA (Cassidy et al., 2006; Lightman and Taylor, 2011). Patients should be followed closely by an ophthalmologist. Cycloplegic agents, steroids, NSAIDs, or immunosuppressive agents are used for uveitic findings (Patel and Lundy, 2002).
5. Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a disease characterized by manifest inflammation in spinal joints and adjacent structures. HLA-B27 is usually positive, RF is usually negative. Therefore, it is located in the group of seronegative spondyloarthropathy (Gouveia et al., 2012).

Typical eye involvement is in the form of sudden unilateral anterior uveitis and this may be the first manifestation of the disease. However, superficial keratitis and corneal ulcers (Fig. 4) may occur (Gouveia et al., 2012).

Marsovsky et al. analyzed central and peripheral langerhans cell number and morphology in AS patients with in vivo confocal microscopy. Langerhans cell density and central langerhans cell morphology (LCM) were found to be larger in patients with AS. This situation could lead to systemic activation by stimulating the immune system (Marsovsky et al., In press). Langerhans cell density, size and shape were found even more in patients with high CRP levels. In this way, a correlation has been shown between LCM and the severity of the disease. Dry eye research was performed in the same study. The report suggested that tear production could be suppressed in patients with active inflammation and this inflammation may cause dry eye (Marsovsky et al., In press).
Ortak et al. have demonstrated that corneal thickness is thinner in AS patients compared to the control group as in other rheumatic diseases. There is a balance between proteinases and proteinase inhibitors. If proteinase activity increases, increasing cytokines break the tear function and corneal stability thus causing existing corneal thinning (Ortak et al., In press). In another study, seronegative (RF-) patients' corneal thickness was thinner than that of seropositive patients (Tascı et al., 2012).

![Fig. 4. Corneal ulcer in patient with Ankylosing spondylitis.](image)

### 6. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease characterized by the accumulation of immune complexes in tissues (Davies and Rao, 2008). The most common ocular finding is CCS (%60). Most patients with SLE develop a secondary Sjogren's syndrome. Corneal epitheliopathy, scarring, ulceration, and filamentary keratitis can all occur secondary to keratoconjunctivitis sicca (Palejwala at al., 2012). Recurrent corneal erosions, punctate keratitis (Fig. 5), corneal stromal infiltration, corneal edema and deep interstitial keratitis can occur in SLE patients. Although vision loss often occurs with retinal and neuroophthalmological involvement. Involvement occurs especially during active disease period (Davies and Rao, 2008).

Non-steroidal anti-inflammatory drugs, corticosteroids, anti-malarial medications, and other immunosuppressive agents are used according to the severity of disease. Generally systemic corticosteroid treatment is started with oral prednisone (1–2mg/kg per day). Immunosuppressive medications include cyclophosphamide, mycophenolate mofetil,
azathioprine, chlorambucil, cyclosporine, and methotrexate (Palejwala et al., 2012). Antimalarial drugs (chloroquine and hydroxychloroquine) are associated with dose-related retinal toxicity. Plasmapheresis can be performed to reduce the levels of circulating immune complexes and antibodies. Rituximab, against the B-cell-specific antigen CD20, has been shown to be useful as a monoclonal therapy. Anti interleukin antibodies and tumor necrosis factor are successfully used (Davies and Rao, 2008).

Adan et al. have reported that they detected bilateral stromal keratitis in a patient with diagnosis of SLE. With slit-lamp corneal opacities which persist despite using corticosteroids and with confocal microscopy crystal-like storage and stromal degradation have been shown (Adan et al., 2004). Yazıcı et al. have studied biomechanical properties of the cornea in SLE patients by using ocular response analyzer (ORA). Corneal hysteresis and corneal resistant factor values in patients with SLE were found to be lower than in the control group. This biomechanical changes cause decrease in intraocular pressure (Yazıcı et al., 2011). Accumulated immune complexes cause lysis in corneal collagen and corneal thinning in SLE as is the case with other connective tissue diseases. In this study, central corneal thickness was found thinner compared to the control group (Yazıcı et al., 2011).

**Fig. 5.** Punctate keratitis patient with systemic lupus erythematosus.
7. Conclusion

As a result, nowadays due to the increasing number of surgical procedures involving the cornea, knowing the corneal symptoms and biomechanical properties in patients with connective tissue and rheumatic diseases before corneal surgery like refractive surgery, has a vital value for patients and their doctors. It will enable surgeons to provide against possible later complications such as corneal melting, corneal ulcers, and peripheral ulcerative keratitis. Special condition should be explained to patients, if necessary, surgery should be abandoned. In this way, complications and time lost will be prevented. To diagnose systemic disease by suspecting corneal manifestations provides early initiation of systemic treatment and quality of life of patients can be increased. In addition, if rheumatologists consult these patients to ophthalmologist, early diagnosis and treatment of eye findings will be possible and it will prevent serious complications.

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