

Ocular Manifestations in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is the most common autoimmune disease. Ocular manifestations of this autoimmune disease vary and are mainly keratoconjunctivitis sicca, episcleritis, scleritis and keratitis. Their appearance, as well as their severity are related to RA chronicity and resistance to therapy. The treatment consists of corticosteroids, NSAIDs and cytotoxic drugs, depending on the type of ocular manifestations and the patient's response to treatment.

Keywords

Rheumatoid Arthritis, Ocular Manifestations, Autoimmunity, Nodules, Red Eye, Sicca, Scleritis, Episcleritis, Schirmer's Test, Corticosteroids, Keratitis

1. Introduction

Rheumatoid arthritis is the most common systemic autoimmune disease, and affects middle age women three times more often than the men in a percentage of 0.5% - 2% of the general population. It is a chronic inflammatory disease characterized by a symmetric sterile and progressive synovitis within joints. The disease is also characterized in 80% of the patients by positive rheumatoid factor but there is also a group of auto-antibodies which are called anti-CCPs and are of great significance for the diagnosis of the disease [1] [2]. Presentation of the disease is often in the 3rd decade with joint swelling, usually of hands. The signs of the disease are symmetrical arthritis of the small joints of the hands typically involving the proximal interphalangeal and sparing the distal interphalangeal joints. Joint instability may result in subluxation and deformities, such as ulnar deviation of the metacarpophalangeal joints [Figure 1]. Less frequent involvements are involvements of feet, shoulders,



Figure 1. Hand radiography with rheumatoid arthritis.

elbows, hips, and cervical spine.

Skin involvement includes subcutaneous nodules over bony prominences, and vasculitis which may cause ulcerations. The complications include pulmonary nodules and fibrosis, multifocal neuropathy, septic arthritis, secondary amyloidosis and carpal tunnel syndrome [2]. The majority of the systemic autoimmune diseases have signs and symptoms from the eye and so does Rheumatoid Arthritis. Approximately 25% of patients will have ocular manifestations like scleritis, episcleritis, keratoconjunctivitis sicca, keratitis, corneal disease and less common by choroiditis, retinal vasculitis, episcleral nodules, retinal detachments and macular edema [1] [3].

2. Ocular Manifestations

Keratoconjunctivitis sicca (dry eye syndrome) is the most common eye sign of RA with a percentage of 10% - 35%. It is caused by infiltration of the lacrimal gland by T and B lymphocytes, leading to a secondary atrophy of the gland which is responsible for the decrease of tears [1] [4]. There is a simple test to perform in order to assess the tear production of the gland which is called Schirmer's test, and it is performed by first drying the tear film, then inserting a Schirmer strip into the lower conjunctival cul-de-sac over the temporal aspect of the lower lid. After 5 min, if the strip measures less than 10 mm of wetting, the lacrimal glands are not functioning correctly. The symptoms and signs of foreign body sensation which is very irritated, and there is also a hyperemia of the conjunctiva (red eye). The patients complain for a burning sensation of the eye, pain and blurred vision. Mucus discharge and crusts are not uncommon. So the dominant findings of Keratoconjunctivitis sicca are two: diminished corneal tear meniscus and abnormal Schirmer's test [2] [3]. The primary goal in managing dry eye is to replenish or preserve the tear film. The treatment is a combination of several actions. The patients should avoid dry environments and the overexposure to the sun. Furthermore, they should wear sunglasses and they should prefer rooms with humidifiers. Finally, they should use natural tear substitutes, in extreme cases occlusion of the lacrimal drainage puncta or tarsorrhaphy may be required in order to eliminate the problem [1].

Episcleritis occurs in 4% - 10% of RA patients. There are two forms of episcleritis: the simple episcleritis and the nodular episcleritis. The nodular is characterized by the presence of subconjunctival nodules that are mobile over the sclera [4] [5]. The simple (diffuse) episcleritis is more common. The symptoms include sudden onset, with mild photophobia and discomfort, no visual impairment. Also mild ache may radiate into cheek-eyebrow-temple. The signs of episcleritis include bright red appearance of the eye with engorged blood vessels [Figure 2]. It is important to mention that dilated vessels may also be related with scleritis to distinguish from the two



Figure 2. Episcleritis.

entities, phenylephrine 2.5% eye drops are used. The instillation of one or two drops in the affected eye will constrict the superficial episcleral vessels but not the deeper sclera vessels caused by episcleritis to blanch while those caused by scleritis remain dilated [1] [4]. Also, there is no tenderness on palpation. In episcleritis, it is self-limited and we can treat it with topical/oral/steroids or NSAIDs. It is important to remember that the initial treatment of episcleritis should be focused on relieving discomfort and stopping progression of the disease [1].

Scleritis occurs with the same percentage as episcleritis does, In RA 4% - 10%. RA is a common cause of Scleritis. Scleritis may be diffuse, nodular, or necrotizing. Patients with non-necrotizing scleritis usually have mild joint disease whereas necrotizing disease tends to affect patients with severe long-standing rheumatoid disease with extra-articular manifestations, most notably rheumatoid nodules. Necrotizing scleritis with inflammation is the most destructive [1] [6]. In addition to the ocular findings in non-necrotizing scleritis, avascular areas of the sclera or necrosis may also be seen, surrounded by sclera edema. The complications are perforation, staphyloma and scleral thinning. Necrotizing scleritis without inflammation is a sign of long-standing RA. Scleritis may have similar symptoms to episcleritis but Scleritis has a gradual onset with a deep, boring pain which may radiate into cheek, eyebrows and temples. Scleritis causes blurred vision and photophobia. Patients may have decreased visual acuity and tender nodules over the sclera. There is more pain than in episcleritis [Figure 3] and also there is tenderness on palpation [5]-[7].

The engorged blood vessels do not blanch when we install phenylephrine drops. Suppressing the globe gently. The Scleritis patient will complain for pain while the Episcleritis-patient will not. The treatment is not the same with the one in Episcleritis, actually there is more acute treatment in scleritis [1]. At first we use topical steroids. If there is non-necrotizing disease then we treat with topical and oral NSAIDs. Because there is a large variation in individual responses to NSAIDs, it is often necessary to try a number of different drugs before to find one that provides adequate relief of symptoms. Also periocular steroid injections may be used in non-necrotizing and necrotizing disease but their effects are usually transient.

Corticosteroids by systemic route used when NSAIDs are contraindicated or ineffective. Cytotoxic/immunomodulatory agents (such as cyclophosphamide, azathioprine, methotrexate, mycophenolatemofetil) are usually necessary if the activity of the disease is not fully controlled with steroids or they are used in order to reduce the dose of corticosteroid in patients requiring long term treatment. Immunosuppressive agents, including inhibitors of calcineurin/Ca-channel cyclosporine and tacrolimus have been used as a long term treatment. Monoclonal antibody/biological agents, such as infliximab and rituximab promising. Infliximab as an antagonist of TNF inhibits the referred factor or serum or on the surface of target cells and suppress the inflammatory process and rituximab as a monoclonal anti-CD20 antibody for B lymphocytes eliminates the specific B memory lymphocytes thereby inhibiting activation of antigen reactive cells preventing their operation to create inflammation [8]. Subconjunctival triamcinolone have been used recently with promising results.

The penetrating scleromalakia is a type of necrotizing scleritis without inflammation, which typically may occur in older women with RA long road. The term penetrating is surprising since the penetrating of the ball is extremely unlikely and the integrity of the bulb remains thin but an intact layer of fibrous tissue. It forms necrosis of the sclera near the limbus without vascular congestion. It has been very slow progress by scleral thinning and uncovering the underlying choroid. The treatment may be effective in the initial stages, otherwise the phthisis of the bulb follow.

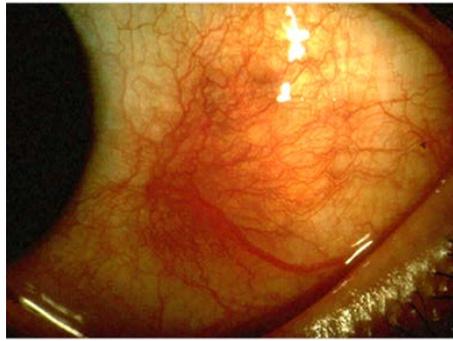


Figure 3. Scleritis.

Keratitis is another very important aspect of the ocular manifestations. Corneal disease in patients with RA can be an isolated complication, but it is most commonly associated with keratoconjunctivitis sicca or a form of anterior scleritis [1] [2]. Keratitis is being characterized by pain with photophobia, foreign body sensation, red eye, tearing and decreased vision. Keratitis is caused by infiltration by inflammatory cells and maybe characterized by corneal opacification or by corneal vascularization, which can lead to ulceration or even more melting of the cornea. Keratitis associated with scleritis may be acute or sclerosing [1]. Peripheral ulcerative keratitis (PUK) is also associated with RA [Figure 4], which may lead to rapid corneal keratolysis, perforation of the globe and visual failure and is associated with systemic vasculitis in more than 50% of cases [9], which carries a high mortality rate and needs early and aggressive treatment. The clinical presentation of PUK is variable, it may present after intraocular surgery or arise de novo, and typically patients describe a non-specific foreign body sensation with pain, a watering eye and reduced visual acuity. The peripheral cornea has morphological and immunological characteristics that predispose to autoimmune inflammation. Unlike the central avascular cornea, the peripheral is provided with nutrients from the capillary, which covered 0.5 mm peripheral cornea. The vascular architecture limbal suitable for IgM accumulation complement C1 and other high molecular weight and immunocomplexes. The deposition of immune complexes triggers the classical complement pathway, which in turn induces chemotaxis of inflammatory cells, particularly neutrophils and macrophages. These cells can release collagenases and other proteases that destroy the corneal stroma. Moreover, the proinflammatory cytokines such as interleukin-1 by these inflammatory cells stimulates stromal keratocytes to produce metalloproteinases, which may accelerate destructive procedure [10]. PUK described local imbalance in the ratio of the levels of a particular collagenase (MMP-1) and the inhibitor (TIMP-1) and it has been suggested that this imbalance is responsible for the rapid keratolysis [11].

Without treatment, the disease maybe is self-limited. Treatment includes NSAIDs are topical/oral/IV corticosteroids and Cytotoxics [7]. Systemic administration of corticosteroids used to treat acute phase and cytotoxic-immunomodulators (cyclo-cyclophosphamide, methotrexate, azathioprine) for long-term treatment. In cases of perforation PUK application corneal tissue glue or amniotic membrane patch or keratoplasty. Systemic administration of cyclosporin as an immunosuppressant, when the RA is in advanced stages in cooperation with the rheumatologist. The local administration of cyclosporin can also have a role, though often may cause local toxicity to the cornea. The decision regarding the duration of treatment depends on whether associated with underlying systemic vasculitis, response to treatment, and whether infection occurred secondly. Particular caution is required when prescribing topical steroids to prevent further thinning of the cornea [1].

RA patients may also develop the following types of non-ulcerative keratitis:

- 1) Peripheral stromal thinning. It is characterized by gradual thinning of the peripheral corneal stroma, leaving the epithelium intact. Perforation can occur in advanced cases.
- 2) Sclerosing keratitis. It is characterized by a gradual thickening and clouding of the corneal stroma adjacent to scleritis.
- 3) Acute central corneal melting. It may occur in association with inflammation or severe eye dryness.

Uveitis (anterior uveitis/iridocyclitis, intermediate uveitis, posterior uveitis/chorioretinitis, panuveitis) is the term used to describe several forms of intraocular inflammation, and may occur in rheumatoid arthritis [Figure 5]. The clinical signs are reduced visual acuity, inflammatory infiltration of the anterior chamber, synechie and miosis [4]. Treatment includes cycloplegics, topical steroids and immunosuppressants [12]. Uveitis may also



Figure 4. PUK (peripheral ulcerative keratitis).



Figure 5. Posterior synechiae.

occur secondary to intraocular inflammation and vasculitis due to scleritis. The posterior scleritis may be accompanied by exudative detachment, swelling and inflammation accompanying orbital elements (prolapse, myositis, limitation of eye movements) [13]. They are referred and other ocular manifestations which are not as frequent for instance macular edema and retinal vasculitis [1] [2] [12].

Moreover, ocular manifestations have been observed as side effects from the use of drugs for RA. Gold causes harmless deposits in the anterior capsule of the lens capsule in about 50% of patients undergoing treatment for more than 3 years.

Substances such as chloroquine and hydroxychloroquine (Plaquenil), used in the treatment of rheumatoid arthritis, may cause toxic maculopathy with reduced visual acuity, and “bull’s eye” in the retina associated with the long duration of treatment (>7-year administration) and the drug dose (mean daily dose to minimize toxicity is 6.5 mg/Kgr body mass for hydroxychloroquine and 5 mg/Kgr body mass to chloroquine) [14]. They are also implicated with the occurrence cornea which is characterized by gold brownish deposits in the lower corneal epithelium. The deposits are reversible in paused administration and do not cause a reduction in visual acuity. Patients may have light halos symptoms. For the early detection of these lesions regular ophthalmological supervision is required every 6 - 12 months with sensitive diagnostic ophthalmic tests.

3. Conclusion

Manifestations of rheumatoid arthritis may affect various components of the eye. There are a lot of signs and symptoms concerning the eye tissue like keratoconjunctivitis sicca, episcleritis, scleritis, keratitis and uveitis. Our study represents a first step in understanding the consequences of rheumatoid arthritis in the eye involvement. Moreover, the purpose of this review article is to clarify to clinicians the possible manifestations of the aforementioned disease, as well as their specific management and treatment options.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this manuscript.

References

- [1] Patel, S.J. and Lundy, D.C. (2002) Ocular Manifestations of Autoimmune Disease. 66.

- [2] Fuerst, D.J., Tanzer, D.J. and Smith, R.E. (1998) Rheumatoid Diseases. *International Ophthalmology Clinics*, **38**, 47-80. <http://dx.doi.org/10.1097/00004397-199803840-00007>
- [3] Shizato, M., Yamamoto, J., Hirata, C.E., Goldberg, C.A., Yoshinari, N.H. and Bonfa, E. (2008) Eye Disease in a Patient with Rheumatoid Arthritis. Vogt-Koyanagi-Harada Syndrome and Rheumatoid Arthritis.
- [4] del Castillo, B.J.M., Diaz-Valle, D., Pato, E., Abad, L.C. and Alejandre, N. (2008) Articular Diseases and Uveitis. *Anales del Sistema Sanitario de Navarra*, **31**.
- [5] Harper, S.L. and Foster, C.S. (1998) The Ocular Manifestations of Rheumatoid Disease. *International Ophthalmology Clinics*, **38**, 1-19. <http://dx.doi.org/10.1097/00004397-199803810-00003>
- [6] McGavin, D.D., Williamson, J., Forrester, J.V., Foulds, W.S., Buchanan, W.W., Dick, W.C., *et al.* (1976) Episcleritis and Scleritis. A Study of Their Clinical Manifestations and Association with Rheumatoid Arthritis. *British Journal of Ophthalmology*, **60**, 192-226. <http://dx.doi.org/10.1136/bjo.60.3.192>
- [7] Galor, A. and Thome, J.E. (2007) Scleritis and Peripheral Ulcerative Keratitis. *Rheumatic Disease Clinics of North America*, **33**, 835-854.
- [8] Morarji, J., *et al.* (2012) Combined Infliximab and Rituximab in Necrotising Scleritis. *Case Reports in Ophthalmology*, **3**, 286-290.
- [9] Sule, A., Balakrishnan, C., Gaitonde, S., Mittal, G., Pathan, E., Gokhale, N.S. and Joshi, V.R. (2002) Rheumatoid Corneal Melt. *Rheumatology*, **41**, 705-706. <http://dx.doi.org/10.1093/rheumatology/41.6.705>
- [10] Yagci, A. (2012) Update on Peripheral Ulcerativekeratitis. *Clinical Ophthalmology*, **6**, 747-754. <http://dx.doi.org/10.2147/OPHTH.S24947>
- [11] Silva, B.L., Cardozo, J.B., Marback, P., Machado, F.C., Galvão, V. and Santiago, M.B. (2010) Peripheral Ulcerative Keratitis: A Serious Complication of Rheumatoid Arthritis. *Rheumatology International*, **30**, 1267-1268.
- [12] Lowder, C.Y. and Char, D. (1984) H. UVEITIS—A Review. *Western Journal of Medicine*, **140**, 421-432.
- [13] Staggos, N. (2002) *Clinical Ophthalmology*, **16**, 444-445.
- [14] Marmor, M.F., Kellner, U., Lai, T.Y., Lyons, J.S. and Mieler, W.F. (2011) American Academy of Ophthalmology. Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy. *Ophthalmology*, **118**, 415-422. <http://dx.doi.org/10.1016/j.ophtha.2010.11.017>



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