Lamba et al., *Cogent Medicine* (2016), 3: 1243771
http://dx.doi.org/10.1080/2331205X.2016.1243771

cogent medicine

OPHTHALMOLOGY | REVIEW ARTICLE

A review of the ocular manifestations of rheumatoid arthritis

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Abstract: *Objectives*: To outline several common ocular complications associated with rheumatoid arthritis. *Findings*: Rheumatoid arthritis is a systemic autoimmune disease that affects approximately 1% of the population worldwide. The synovial membranes of joints are primarily affected; however, rheumatoid arthritis can also manifest in other organs, such as the eye. *Conclusions*: We emphasize the need for timely diagnosis and treatment of rheumatoid arthritis in order to prevent vision-threatening consequences.

Subjects: Allergology & Clinical Immunology; Ophthalmology; Rheumatology

Keywords: complications; ocular inflammation; rheumatoid arthritis

Received: 18 May 2016
Accepted: 15 September 2016
First Published: 06 October 2016

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Reviewing editor:
Maren Klemm, Universitatsklinikum Hamburg-Eppendorf, Germany

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease that is characterized by significant inflammation of the synovial membrane of joints. The cardinal joint manifestations of this disease include pain, swelling, and tenderness followed by cartilage destruction, bone erosion, and eventually joint deformities (Harper & Foster, 1998).

Rheumatoid arthritis is the most common systemic autoimmune disease, affecting approximately 1% of the population. Women are three times more likely to be affected than men, with 80% of patients developing the disease between the ages of 35 and 50 (Widdifield et al., 2014). RA is a systemic disease; therefore, many patients exhibit extra-articular manifestations (Feldmann, Brennan, & Maini, 1996; Moreland & Curtis, 2009).

Despite exhaustive research, the precise cause of RA remains unknown. Although a variety of cells play a role in RA disease, macrophages may be of particular significance in the disease process. Pro-inflammatory cytokines secreted by macrophages, such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6), are believed to have a critically important role in the induction and propagation of chronic inflammation (Moreland & Curtis, 2009). TNF-α is found to be

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PUBLIC INTEREST STATEMENT

This article describes several ocular complications known to be associated with rheumatoid arthritis (RA). Ocular manifestations of RA includekeratoconjunctivitis sicca (dry eye syndrome), episcleritis, scleritis, peripheral ulcerative keratitis and retinal vasculitis. If these ocular diseases are not promptly addressed, there is a high potential for patients to suffer permanent damage and blindness. We emphasize the need for collaborative efforts between ophthalmologists and rheumatologists when evaluating and treating patients with RA.

overproduced in joints of patients with RA and can induce increases in synoviocyte proliferation and a cascade of secondary mediators involved in the recruitment of inflammatory cells. Joint erosion is known to occur early in RA, affecting about 40% of the patients during the first year and 90% during the first two years (Camussi & Lupia, 1998; Plant, Jones, Saklatvala, Ollier, & Dawes, 1998).

Patients with RA who have high titers of rheumatoid factor are most likely to have extra-articular manifestations of their disease, including rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications (Hochberg, Johnston, & John, 2008; Turesson, O'Fallon, Crowson, Gabriel, & Matteson, 2003).

2. Ocular manifestations

2.1. Keratoconjunctivitis sicca

Keratoconjunctivitis sicca, or dry eye syndrome, is commonly seen in patients suffering from systemic autoimmune disease, and RA is the most common autoimmune disorder associated with dry eye (Tong, Thumboo, Tan, Wong, & Albani, 2014). Rheumatoid arthritis patients with dry eye commonly develop dry eye secondary to lymphocytic and plasma cell infiltrate of the lacrimal gland that lead to destruction of acini in the lacrimal glands. Characteristic complaints include itching, burning, foreign body sensation, and photophobia. The severity of the symptoms correlates with the age and duration of RA, but does not correlate with the severity of arthritis. Use of artificial tear substitutes and punctal plugs are usually necessary to counter the symptoms of severe dry eye in patients with RA. Topical Cyclosporine A (CsA) is approved by the FDA for the treatment of dry eye. Cyclosporine A is a fungal-derived peptide that inhibits T-cell activation and consequently inhibits the inflammatory cytokine production seen on the ocular surface of patients with dry eye and RA (Kunert, Tisdale, Stern, Smith, & Gipson, 2000; Pepose, Akata, Pflugfelder, & Voigt, 1990; Tong et al., 2014).

2.2. Episcleritis

Episcleritis is the inflammation of superficial layers of sclera. Episcleritis presents as a relatively asymptomatic acute onset injection in one or both eyes. Other symptoms may include eye pain, photophobia, and watery discharge. Its prevalence among patients with RA has been reported to be 0.17–3.7%. Rheumatoid episcleritis affects women more frequently than men, and is most common in the sixth decade of life. Most cases of episcleritis are self-limiting, but patients may find some relief with topical lubricants, nonsteroidal anti-inflammatory agents, or corticosteroids. If unresponsive to topical therapy, systemic nonsteroidal anti-inflammatory agents may be useful (Sainz de la Maza et al., 2012).

2.3. Scleritis

Anterior scleritis is a painful and potentially blinding inflammatory disease that presents with a characteristic violet-bluish hue with scleral edema and dilatation. With posterior scleritis, patients may present with a white eye, but with severe retrobulbar pain. Fundus exam may also reveal chorioretinal granulomas, retinal vasculitis, serous retinal detachment and optic nerve edema with or without cotton-wool spots (Lyne & Pitkeathley, 1968; McGavin et al., 1976).

Although scleritis may be the initial sign of rheumatoid disease, it usually presents more than ten years after the onset of arthritis. Multiple studies have found that patients with scleritis have more advanced joint disease and more extra-articular manifestations than do rheumatoid patients without scleritis (Jayson & Jones, 1971; Lyne & Pitkeathley, 1968; McGavin et al., 1976; Sainz de la Maza, Foster, & Jabbur, 1994; Sevel, 1967). Although subcutaneous nodules appear in 20–30% of patient with RA, their presence increases to approximately 50% in patients with scleritis (McGavin et al., 1976). Pulmonary disorders, such as pleural effusion, lung nodules, pneumonia are more common in rheumatoid patients with scleritis than in patients who do not have scleritis. In addition, cardiac manifestations, including pericarditis, valvular disease, conduction abnormalities, and myocardial ischemia are more common in RA patients who have a history of scleritis (Jayson & Jones, 1971; Kleiner, Raber, & Passero, 1984; McGavin et al., 1976; Sainz de la Maza et al., 1994). Exacerbation

of scleritis often occurs at times of increased RA activity (Foster, Forstot, & Wilson, 1984; Jayson & Jones, 1971; Lyne & Pitkeathley, 1968; Sevel, 1967).

Scleromalacia perforans is a rare form of necrotizing anterior scleritis. It presents with progressive thinning of the sclera without significant redness or pain. The blue-black hue of the sclera is a result of the melanocyte-laden choroidal layer of the eye becoming visible through the thin sclera (Sims, 2012).

The mortality rate is higher in patients with RA with scleritis when compared to patients with RA without scleritis (Foster et al., 1984; McGavin et al., 1976) 36–45% of patients with scleritis and RA will be dead within three years of the onset of scleritis if left untreated with systemic medications. This compares to a three year mortality rate of 18% in RA patients without scleritis. Death is usually secondary to extra-articular vasculitis. Necrotizing scleritis is associated with a higher mortality then the other forms (Foster et al., 1984; Jayson & Jones, 1971; Sevel, 1967).

Treatment of scleritis almost always requires systemic therapy, as topical therapy is generally insufficient. The use of nonsteroidal anti-inflammatory drugs, corticosteroids, or immunomodulatory drugs is usually necessary in the treatment of scleritis (Foster et al., 1984).

2.4. Peripheral ulcerative keratitis (PUK)

Peripheral ulcerative keratitis (PUK) refers to a crescent shaped destructive inflammation of the juxtalimbal corneal stroma associated with an epithelial defect, presence of stromal inflammatory cells, and stromal degradation. It is a destructive process mediated by collagenolytic and proteolytic enzymes released from neutrophils and/or macrophages that results in peripheral corneal stromal degradation. Patients with PUK frequently present with pain, tearing and photophobia. Although topical management may lead to some symptomatic relief, the main treatment of PUK is the treatment of the underlying systemic vasculitis (Foster, 1980; Messmer & Foster, 1995, 1999; Stern, 2011).

2.5. Retinal vasculitis

RA can be associated with retinal vascular inflammation, which is a serious and potentially blinding condition. Retinal vasculitis is generally painless and patients may be asymptomatic or present with a variety of symptoms, including decreased visual acuity, visual floaters, scotomas, decreased ability to distinguish colors, and metamorphopsia (Murray & Rahi, 1984). Active vascular disease is characterized by exudates around retinal vessels resulting in white sheathing or cuffing of the affected vessels. However, many patients may show no clinical signs on exam, and fundus fluorescein angiography may be necessary to detect areas of retinal swelling, exudation, and macular edema. Severe retinal vasculitis requires adequate inflammation control using corticosteroids or immunomodulatory therapy (Androudi et al., 2013; Giordano et al., 1990; Matsuo, Masuda, & Matsuo, 1998; Wilkinson & Torrance, 1967).

3. Conclusion

RA is associated with many extra-articular manifestations, which include ocular diseases such as keratoconjunctivitis sicca, episcleritis, scleritis, peripheral ulcerative keratitis, and retinal vasculitis. These concomitant ocular manifestations are of utmost concern and must be addressed because of the high potential for permanent damage and blindness if they are allowed to run their course without intervention. Collaborative efforts between the ophthalmologists and rheumatologists involved in the evaluation and treatment of patients with RA are essential to effectively manage any ocular complications that may arise.

Funding
This work was financially supported by Consultancies with Aldeyra Therapeutics (Lexington, MA), Bausch & Lomb Surgical, Inc (Rancho Cucamonga, CA), Eyegate Pharma (Waltham, MA), Novartis (Cambridge, MA), pSivida (Watertown, MA), and Xoma (Berkeley, CA). Grants or grants pending with Alcon (Aliso Viejo, CA), Aldeyra Therapeutics (Lexington, MA), Bausch & Lomb (Bridgewater, NJ), Clearside Biomedical (Alpharetta, GA), Dompé pharmaceutical (Milan, Italy), Eyegate Pharma (Waltham, MA), Icon (Dublin, Ireland), Novartis Pharmaceuticals (Cambridge, MA), pSivida (Watertown, MA), Santen (Osaka, Japan), Xoma (Berkeley, CA). Payment for lectures including service on speaking bureaus: Alcon (Aliso Viejo, CA), Allergan (Dublin, Ireland). Stock or Stock Options: Eyegate Pharma (Waltham, MA).

Competing Interests
The authors declare no competing interest.

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Citation information
Cite this article as: A review of the ocular manifestations of rheumatoid arthritis, Neerav Lamba, Stacey Lee, Hina Chaudhry & C. Stephen Foster, *Cogent Medicine* (2016), 3: 1243771.

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