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REVIEW

Ocular manifestations of rheumatic diseases

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Abstract
Purpose Our aim was to summarize key aspects of the pathomechanism and the ocular involvements of rheumatic and systemic autoimmune diseases.
Methods Apart from a paper in French (Morax V, Ann Oculist 109:368–370, 1893), all papers referred to in this article were published in English. All the materials were peer-reviewed full-text papers, letters, reviews, or book chapters obtained through a literature search of the PubMed database using the keywords ocular manifestations; pathogenesis; systemic inflammatory rheumatic diseases; rheumatoid arthritis; osteoarthritis; fibromyalgia; systemic lupus erythematosus; seronegative spondyloarthritis; ankylosing spondylitis; reactive arthritis; enteropathic arthritis; psoriatic arthritis; systemic sclerosis; polymyalgia rheumatica and covering all years available. Some statements articulated in this paper reflect the clinical experience of the authors in their tertiary-referral center.
Results Ophthalmic disorders are categorized by anatomical subgroups in all rheumatic diseases. The most common ocular manifestations are diverse types of inflammations of different tissues and dry eye disease (DED).
Conclusion The eye could be a responsive marker for the onset or aggravation of an immune reactivation in many rheumatic diseases, furthermore, ocular findings can antedate the diagnosis of the underlying rheumatic disease. By recognizing ocular manifestations of systemic rheumatic diseases it might be possible to avoid or at least delay many long term sequelae.

Keywords Ocular manifestations · Pathogenesis · Systemic inflammatory rheumatic diseases · Rheumatoid arthritis · Fibromyalgia · Systemic lupus erythematosus · Psoriatic arthritis · Spondyloarthritis · Reactive arthritis · Scleroderma · Polymyalgia rheumatica

Introduction

Most of the inflammatory rheumatic diseases are systemic conditions with several clinical and pathological manifestations outside of the joints. The eye has a distinguished innate and adaptive immune system underpinned by even the presence of the

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blood–retina barrier and the alymphatic status of its inner structure. The liquid components of the eye, namely the aqueous and vitreous humors, are separated from the blood by tight junctions (occluding junctions or zonulae occludentes) [1], which contribute to maintaining the ideal microenvironment of the eyeball. Inflammatory rheumatic diseases can have destructive effects since as a consequence of vascular abnormality immunoregulatory molecules present in ocular fluids are changed and *milieu interieur* inside the eye is modulated.

Not only ophthalmologically may the identification of ocular signs and symptoms be of importance, but ocular inflammation could also be a sensitive marker for the severity of the systemic condition; moreover, ocular involvement can antedate exacerbation of an immune reaction in many systemic diseases. Hence, knowledge of ocular manifestations of rheumatic diseases is indispensable for both rheumatologists and immunologists. This review article intends to resume the key pathogenic events, as well as to depict ophthalmologic manifestations of rheumatic diseases.

Rheumatoid arthritis (RA)

RA is a chronic autoimmune inflammatory disease of unknown origin marked by joint swelling, joint tenderness, and destruction of synovial joints, resulting in severe disability and premature mortality [2]. Concerning ocular manifestations of RA, we have to lay down that the anterior segment is more commonly affected compared to the posterior segment.

Cornea

A wide range of corneal manifestations can occur in RA. Corneal involvement can be definitely sight-threatening mainly in case of an overlying infection. Aggressive intravenous antibiotics should be considered in addition to local eye drops in the case of patients on biologic agents for corneal ulcer [3].

Episcleritis/scleritis/uveitis

Episcleritis (Fig. 1) and scleritis can be manifestations of RA and vice versa the etiology of these alterations is often a connective tissue disease, and RA is the commonest. When the clinical data of a large

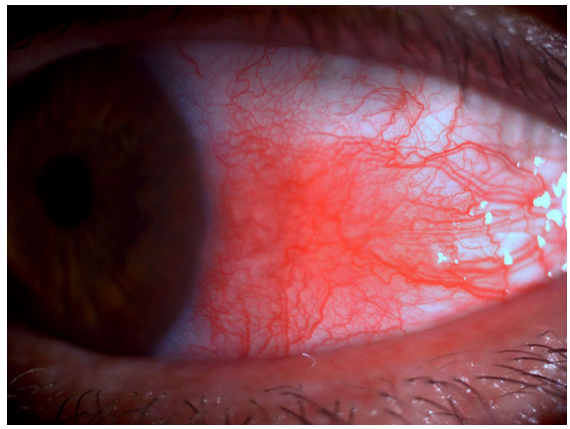

Fig. 1 Extensive episcleritis with dilated blood vessels at the temporal region in an RA patient

population presenting with uveitis and/or scleritis were reviewed, the origin of these ocular complications was found to be 5% autoimmune, 15% autoinflammatory and 14% mixed autoimmune/auto-inflammatory. The term "autoimmune uveitis" [4] should not be used as a synonym for intraocular inflammation of non-infectious origin, just be reserved for intraocular inflammations of confirmed autoimmune origin. Anti-cyclic citrullinated (anti-CCP) peptide is an important diagnostic and prognostic tool for RA, since out of all laboratory parameters, the level of this antibody was significantly associated with ocular manifestations in RA [5].

Dry eye disease (DED)

Is there ever such a great variability in the prevalence of lacrimal gland involvement in RA, DED can surely be regarded as its most common ocular involvement often noticed in patients when the underlying disease is associated with Sjögren's syndrome (SS). The analysis of the data of 143 consecutive RA patients found that 45% of them had subjective symptoms and 38% had objective signs of DED [6]. As for gender characteristics of DED in RA, women are 9 times more commonly affected than men [7].

Choroid

Kurt et al. demonstrated decreased corneal thickness (CT) of 59 RA patients compared to healthy controls. However, no significant correlation was found

between CT measurements and Disease Activity Score 28 (DAS 28) or Larsen disease activity scores [8].

Osteoarthritis (OA)

By definition, OA or degenerative arthritis is a complex condition characterized by focal areas of loss of articular cartilage within the synovial joints, associated with simultaneous hypertrophy of the bone and thickening of the capsule, resulting in substantial pain and disability.

Retina

Age-related macular degeneration (AMD) is the major cause of blindness in developed countries [9]. AMD is strongly associated with aging; there is extreme involvement of the extracellular matrix in its pathophysiology and implication of the complement pathway of the innate immune system [10]. A survey of the epidemiologic relationship between AMD and OA patients found that AMD patients did not have a higher risk for OA formation, while a modestly increased risk for the appearance of neovascular AMD was noticed in patients with OA as well as RA perhaps due to medical treatments for the underlying disease [11].

Fibromyalgia (FM)

FM is a complex condition with widespread chronic musculoskeletal pain, which is accompanied by a range of other symptoms including fatigue, poor sleep, memory issues, and depression [12].

FM independently or together with depression and neuroticism contributes to the development of primary SS-associated fatigue, and therefore DED could be mentioned as its elementary ocular sign [13].

Concerning its further ocular manifestations, a case report was presented by Tenkman et al. of a fifty-plus female with definite keratoconus (KC)—an ectatic disorder of the cornea which produces progressive thinning—in the one eye and a possible KC in the fellow eye [14]. The patient was without a family history of KC or any connective tissue disease for that matter other than FM [15].

Systemic lupus erythematosus (SLE) or lupus

SLE or simply lupus is a highly heterogeneous chronic autoimmune disease with undefined etiology in which the body's immune system mistakenly attacks healthy tissues [16]. It is predominantly women, who can be affected in their childbearing age.

Orbital involvement

Extraocular muscles can be inflamed, and even inflammatory pseudotumor can develop, the diagnosis of which can be delayed by reason of simultaneous immunosuppressive and low dose oral corticosteroid therapy [17]. An uncommon clinical presence in the SLE spectrum is panniculitis, also called lupus erythematosus profundus which is presented in a case report as masked by an accompanying idiopathic orbital inflammatory syndrome (IOIS), a nonspecific inflammation of orbital tissue, which is typically manifest in SLE.

Eyelid

In SLE, typically in lower eyelids, a specific, irritating, discrete, slightly raised erythematous scaly plaque called discoid lupus-type rash can appear, which may be complicated by scar formation, scaling and madarosis, or sometimes dyspigmentation [18]. Topical corticosteroids and oral antimalarial drugs can be administered in these cases.

Cornea and DED

DED is the most frequent ocular manifestation of SLE occurring in one-third of patients because of the involvement of both the main and the accessory lacrimal glands [19]. Besides DED, a wide range of corneal alterations can be found ranging from superficial punctate keratitis through stromal infiltration to peripheral ulcerative keratitis [18].

Episcleritis and scleritis

Episcleritis and scleritis may be identified as unusual involvements in SLE; nevertheless, they can be predictive signs of an active status. Both of them can be initial findings followed by other ocular manifestations in SLE, especially in the case of the latter,

which is often underdiagnosed although it may be more severe with enduring visual impairment [20].

Retinal and choroidal changes

The prevalence of retinal abnormalities ranges from 3 to 29% depending on the examined population and the disease stage; the previous value represents the well-controlled patients, while the latter is attributed to patients with a more active underlying disease. Mostly, central arterial occlusions can be seen, but there are several cases describing combined central retinal artery and vein occlusion even in a bilateral form [21]. An unusual form of retinal vascular alterations is the Purtscher's retinopathy, the pathogenesis of which is based on embolic occlusions of the precapillary arterioles caused by increased intracranial/intrathoracic pressure and secondary extravasation of fluid [22]. Choroidopathy is less frequent compared to retinopathy and can be detected by indocyanine green angiography (ICG-A). This diagnostic tool could be useful in the screening of patients with SLE to decide whether to perform a renal biopsy or not since, according to a study, the deformations of choroidopathy by ICG-A could be an indirect sign of renal involvement [23].

Seronegative spondyloarthritis or seronegative spondylarthropathies (SpA)

SpA is an umbrella term for rheumatic diseases marked by axial and/or peripheral arthritis. As they are associated with enthesitis, dactylitis, and potential extra-articular manifestations, several subtypes are distinguished.

Ankylosing spondylitis (AS)

Unequivocally acute anterior uveitis (Fig. 2) is considered to be the most frequent ocular manifestation of AS since its prevalence is at least 30% of cases with a frequency peak of 33.4% [24]. AS plays an important role in the etiology of uveitis since the analysis of the data of 1916 uveitic patients found AS to be the second most frequent cause of uveitis with 16.8%, followed by HLA-B27-positivity, representing 15.4% of patients [25].

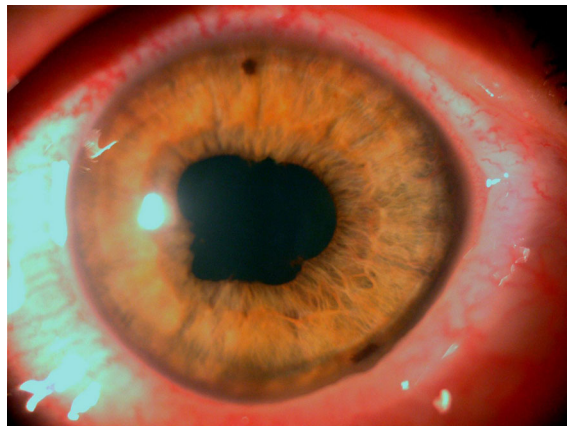

Fig. 2 Chronic anterior uveitis with dilated conjunctival blood vessels and deformed pupil due to anterior synechiae

Since AS can affect both the anterior and the posterior segments of the eye, diversified manifestations can occur, such as posterior synechiae, cataracts, elevated intraocular pressure with or without glaucoma, keratic precipitates, macular edema, and hypopyon in 5–50% of patients [25]. In a study carried out among HLA-B27-associated uveitic patients, the most frequent involvement was diffuse vitritis (93.1%) followed by papillitis (82.7%). Cystoid macular edema (37.9%) and epiretinal membrane (17.2%) along with retinal vasculitis (24.1%) also appeared among them. The fact that 32% of patients needed systemic immunosuppressive therapy for their inflammation is to be taken into consideration [26].

Reactive arthritis (ReA)

ReA is characterized by additive or migratory oligoarthritis, which is associated with extra-articular symptoms that distinctively follow a gastrointestinal or urogenital infection by a minimum of 1 to a maximum of 3–6 weeks. The first case of ReA reported in 1918 was a 16-year-old young male with the classical triad of arthritis, urethritis, and conjunctivitis followed by iritis and keratitis [27].

Surveying clinical data of 25 patients with ReA uveitis (84%), scleritis (3%), and conjunctivitis (2%) were found as ocular signs at the time of diagnosis, but during the follow-up period ocular complications altered as the leading manifestation was conjunctivitis (96%), followed by anterior uveitis (92%). The fact that should be accentuated is that not only anterior

segment inflammations such as keratitis (64%) and scleritis (28%) were seen, but also posterior segment inflammations such as posterior uveitis (64%), intermediate uveitis (40%), papillitis (16%) too; moreover, other anomalies, namely cystoid macular edema (28%), cataract (56%), and glaucoma (16%), were also found in a relevant rate [28].

Enteropathic arthritis

Enteropathic arthritis predominantly occurs on the basis of an IBD (Crohn's disease (CD) or ulcerative colitis (UC)). Within the extra-intestinal complications of IBD, the frequency of ophthalmic complications (OC) features 2–6%, and CD patients are more intensely exposed [29]. Episcleritis and anterior uveitis are well-known extra-intestinal manifestations of CD. Posterior scleritis is an extremely rare condition that may be idiopathic or related to collagen vascular diseases [30].

Psoriatic arthritis (PsA)

Historically, an ocular manifestation in PsA was first reported by Morax in 1893 in a 37-year-old male patient with arthritis and psoriasis who developed unilateral iritis and hypopyon [31]. Lambert and Wright investigated 112 PsA patients and found that 31.25% of them had ocular changes. The leading alteration was conjunctivitis (19.6%) followed by iritis (7.1%), DED (2.7%), and episcleritis (1.8%) [32]. The association of posterior scleritis with PsA was demonstrated for the first time by Altan-Yaycioglu and coworkers with the case of a 74-year-old female patient. Oral azathioprine and prednisone therapy was initiated, and it resolved her problem, although 4 months later her scleritis recurred [33].

Drawing a comparison between ocular manifestations of psoriasis and PsA, the latter group has more ocular complications than the previous one [34].

Undifferentiated spondyloarthritis

Up to 40–82% of acute anterior uveitis (AAU) is associated with the HLA-B27 allele [35], which is strongly connected to SpAs. A large, observational case series study including 175 patients with HLA-B27-associated AAU was investigated, and 21 (12%) of them were diagnosed with undifferentiated spondyloarthropathies [36].

Juvenile onset spondyloarthritis

This term is used for SpAs under 17 years of age. A remarkable case series study was described by Menkes et al.; 31 of their 35 cases were boys, and during the course of the study typical as well as possible ASs were investigated, and five patients had ocular manifestations [37].

Scleroderma or systemic sclerosis (SSc)

Scleroderma or systemic sclerosis (SSc) is a chronic, systemic, connective tissue disease of unknown origin traditionally divided into two subgroups: limited cutaneous (lcSS) and diffuse cutaneous (dcSS) types.

Eyelid involvement

Various clinical signs can occur: eyelid stiffness, eversion, lagophthalmos, blepharophimosis, loss of eyelashes, and sometimes eyebrows, i.e., ciliary madarosis which is mainly present in dcSSc [38]. As for vasculopathy, it is manifested in the form of telangiectasia and it is perceived in 17–21% of patients, typically together with telangiectasia located elsewhere on the face (Fig. 3) [39].

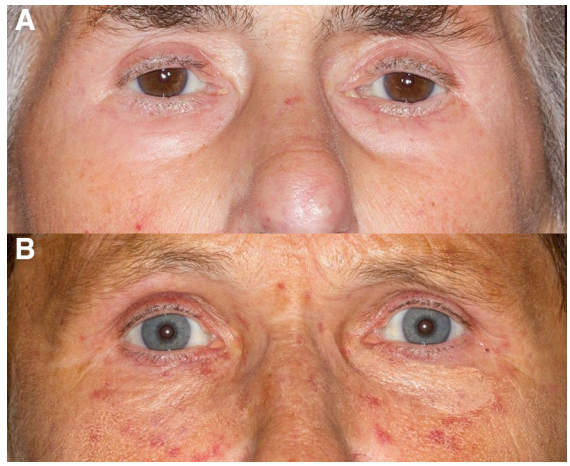

Fig. 3 Blepharophimosis, ciliary madarosis (**a**) and telangiectasia (**b**) on the eyelids of SSc patients

Conjunctiva/episclera

Being a richly vascularized tissue, conjunctiva is highly affected by vasculopathy, which is realized as obliteration of the microvasculature, compensatory angiogenesis, telangiectasia, intravascular sludging, or loss of vessels [40].

DED

DED is thought to be the most common ocular manifestation of SSc followed by eyelid skin deformations [41]. Şahin and co-workers declared that beyond the fact that corneas of SSc patients are thinner compared with those of normal controls, coexistence of DED induces an additional decrease in corneal thickness [42]. SSc patients only realize their DED symptoms after a longer period of the disease as proved by a study examining objective signs and subjective symptoms of DED in SSc patients [43].

Iris

One of the most characteristic features in iris is transillumination, i.e., atrophy, which is an abnormality of the iris epithelium and identified as a consequence of imperfection of the epithelium [41]. Two factors, the iris being a part of the uveal tract plus widespread small vessel vasculopathy being one of the main pathomechanisms in SSc, account for the presence of manifestations affecting the iris [38].

Retina/choroid

The first case report about retinal changes in SSc was published in 1953 by Agatston detecting retinal cystoid bodies in an SSc patient [44]. Other heterogeneous retinal abnormalities have already been observed for several decades like soft and hard exudates, neuroretinal edema, hemorrhages, fibrinoid changes, and lipid deposits [45]. Most of them are described in dcSSc, and as advanced or difficult cases it could be problematic to distinguish them from signs of hypertensive retinopathy.

Polymyalgia rheumatica (PMR)

Polymyalgia rheumatica (PMR) is an inflammatory condition of unknown origin characterized by pain or stiffness in the cervical region, shoulders, and upper arms mostly, but it may occur all over the body.

The first mention of a possible association between PMR and an ocular manifestation, namely scleritis, was by Tuft and Watson who reviewed the clinical features of 290 patients with scleral inflammation and found 2 diffuse anterior scleritis cases associated with PMR [46]. The highest number of patients with ocular involvements of PMR was described by Faez et al. who processed 7 cases with scleritis or uveitis. What deserves attention in their work is that 2 out of 7 cases were panuveitis and in one patient uveitis developed 2 months before PMR was actually diagnosed [47]. One case highlights the challenging diagnostic nature of Wegener's granulomatosis (WG) that may evolve on a background of PMR, and for this reason undifferentiated ocular inflammatory syndromes should raise the suspicion of WG [48].

Conclusions

Because of its anatomical structure and privileged immune system, the eye is susceptible to immunologic disorders, vascular irregularities, and different kinds of inflammations. It could be a responsive marker for the onset or aggravation of an immune reactivation in many rheumatic diseases; moreover, ocular findings can precede the diagnosis of the underlying rheumatic disease. With this end in view, one should not extenuate extra-articular manifestations. By recognizing ocular manifestations of systemic rheumatic diseases, it might be possible to avoid or at least delay many long-term sequelae.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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