Ocular manifestations of the potentially lethal rheumatologic and vasculitic disorders

Les manifestations oculaires des troubles rhumatologiques et vasculaires potentiellement mortels

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Summary  Vision threatening ocular inflammation may occur in patients with any of the acquired connective tissue disorders and vasculitic diseases. Additionally, the ocular inflammation may be the presenting manifestation of the disease, which leads the patient to seek medical care. Other manifestations of the potentially lethal disease may be subtle or absent, presenting the thoughtful ophthalmologist with the opportunity to make life saving discoveries. Necrotizing scleritis, peripheral ulcerative keratitis, and retinal vasculitis are the ocular findings which should prompt the ophthalmologist to initiate very aggressive measures aimed at discovering any evidence of extra-ocular abnormalities, laboratory or otherwise. Appropriate therapy will be sight saving and may be life saving.

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Résumé  Une inflammation oculaire qui atteint la vue peut se produire chez n’importe quel patient ayant des troubles acquis du tissu conjonctif et des maladies vasculaires. De plus, l’inflammation oculaire peut être le premier symptôme de la maladie qui amène le patient à consulter. Les autres symptômes du trouble potentiellement mortel peuvent être légers ou absents mais les ophthamologues consciencieux peuvent décéler des pathologies graves, pouvant sauver des vies. Sclérite nécrosante, kératite ulcéropériphérique et vascularite rétinienne sont des signes qui doivent mener l’ophthalmologue à dépister en urgence des anomalies extraoculaires, biologiques ou d’autre type. Des traitements appropriés peuvent permettre de sauver la vision mais aussi la vie.

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Introduction

The fact that the eyes of patients with the acquired rheumatic diseases can develop problems has been apparent to ophthalmologists for over a century. What has become evident more recently is the fact that some of the problems, which patients with such disease may develop, are harbingers of potentially lethal yet occult manifestations of a worsening of the disease in other organs. Not all ocular involvement in the rheumatic diseases reflects such potentially lethal disease transformation, of course, and the development of keratoconjunctivitis sicca or episcleritis in a patient with rheumatoid arthritis is no reason for alarm. In fact, even the development of diffuse or sectoral scleritis should not be overly alarming, although the treatment of the patient who develops scleritis almost certainly will have to be changed in order to appropriately tend to the eye. The onset, however, of necrotizing scleritis (NS) (Fig. 1) or of peripheral ulcerative keratitis (PUK) (Fig. 2) in a patient with rheumatoid arthritis is an entirely different matter.

The evidence is abundant in peer-reviewed literature that the onset of one of these two lesions is commonly an indication that the patient’s predominantly articular inflammatory disease has now transformed into a systemic microvasculitic disease [1–5]. The challenge for the ophthalmologist in such a circumstance is two-fold:

- developing a therapeutic strategy which will save the eye and preserve vision;
- convincing the rheumatologist of the systemic implications for this new development of NS or PUK.

It is this latter matter, which is sometimes the more challenging, since the rheumatologist may feel quite confident that, from the rheumatologic perspective, the patient’s disease is stable or “burned out”. The ophthalmologist may need to provide to the rheumatologist copies of the papers, which have appeared in peer-reviewed literature, which attest to the fact that the patient’s life may be in jeopardy unless considerably more vigorous systemic therapy is employed. Such therapy of course, almost certainly will be to the advantage of the ophthalmologist in getting the ocular inflammatory disease into remission.

Rheumatoid arthritis

Both necrotizing scleritis and peripheral ulcerative keratitis in a patient with rheumatoid arthritis represent ocular vasculitic lesions. Histopathologic studies attest to this fact, [6] and the tissue ischemia and necrosis, which ensue, can never be stopped through local strategies alone. Of course, local adjunctive care is appropriate, and commonly includes the use of topical and systemic anti-collagenolytic agents (medroxyprogesterone, 1%, drops; doxycycline, 100 mg po bid) topical antibiotic, conjunctival resection, employment of cyanoacrylate tissue adhesive, corneal and/or scleral grafting, etc. But it is to be emphasized that the ophthalmologist will be engaged in a fool’s errand if he or she relies solely on such local ocular care in hopes of curing the patient’s problem (Fig. 3). Such care will never succeed and must always be accompanied by a change in the

Figure 1. Necrotizing scleritis in a patient with rheumatoid arthritis in the absence of active arthritis. This is an ominous signal of occult, underlying, potentially lethal systemic vasculitis.

Figure 2. Peripheral ulcerative keratitis in a patient with rheumatoid arthritis. This too is an ominous sign indicative of potentially lethal occult systemic vasculitis.

Figure 3. Necrotizing scleritis and peripheral ulcerative keratitis in a patient with rheumatoid arthritis. Note the folly of attempts at support from scleral grafting in the absence of systemic control of the underlying disease.
patient’s systemic therapy, most particularly with vigorous immunomodulatory therapy [7–9].

We conducted a prospective, longitudinal, non-randomized cohort study of 34 patients with rheumatoid arthritis who developed destructive ocular inflammatory lesions in the form of necrotizing scleritis and/or peripheral ulcerative keratitis [2]. All 34 patients received comparable local ocular care. Seventeen of the patients were also treated with systemic immunomodulatory therapy, while the other 17 were not. The ocular outcomes were predictable, based upon the vast experience of many others over the past 50 years [3,5,10], with progression of scleritis or of peripheral keratitis occurring in 13 of the 17 patients who were not immunosuppressed, and in none of the 17 patients who received immunosuppressive chemotherapy. Five patients receiving conventional therapy also developed extra-articular vasculitic lesions, and 54% of this group had died from such lesions within 8 years of the onset of a necrotizing scleritis or peripheral ulcerative keratitis. No patient on immunomodulatory therapy died. One patient in the immunosuppressive therapy group had episodic abdominal pain, which was blamed on the patient’s cyclophosphamide, which was withdrawn. The patient subsequently died of a perforated bowel, and on autopsy was found to have widespread vasculitic lesions of the mesentery and of the bowel, with bowel perforation.

It is not at all clear why, but is abundantly clear that the eye is a sensitive barometer for subclinical rheumatoid arthritis associated vasculitis. The appearance of necrotizing scleritis or of peripheral ulcerative keratitis in a patient with rheumatoid arthritis should be taken as an indicator of slowly emerging potentially lethal visceral vasculitis lesions, and it is incumbent upon the ophthalmologist to make certain that the rheumatologist caring for the patient is made aware of the literature on this matter, as referenced above [7–9].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) may also be lethal, and when it is, it is generally as a consequence of kidney or of central nervous system disease. The development of discoid lupus blepharitis, or of conjunctivitis or episcleritis or even scleritis in a patient with established systemic lupus erythematosus is of little concern from the standpoint of a transformation of the systemic characteristics of this disease, although such ocular inflammatory manifestations do require their own therapy. Necrotizing scleritis rarely occurs in the patient with systemic lupus erythematosus, and this is also true for peripheral ulcerative keratitis, although patients with SLE can develop peripheral keratitis. Patients with SLE may also develop uveitis, although this is not a common manifestation of ocular inflammatory disease in lupus. Rather, it is the retinal vasculitis and choroidopathy that is the harbinger of a transformation in the characteristics of SLE. The following case example will be illustrative of this phenomenon.

A 30-year-old Asian female had been diagnosed with systemic lupus erythematosus and was treated with hydroxychloroquin and daily corticosteroid therapy. She, however, developed progressive bilateral vision loss in the 20 days prior to her admission to the Massachusetts General Hospital in Boston, Massachusetts, USA. I was summoned for consultation and upon evaluation found her visual acuities to be 20/400 right eye and 20/200 left eye. The anterior segment examination was unremarkable. However, dilated funduscopic examination disclosed widespread evidence of lupus retinopathy, with retinal infarcts and hemorrhage (Fig. 4). Fluorescein angiography disclosed the expected diagnostic features of late vessel staining, i.e., the patient had classic retinal vasculitis with retinal infarcts (Fig. 5). Pulsed sequential plasmaphoresis and intravenous cyclophosphamide therapy was begun because of the urgency of this matter, with the recognition that severe retinal vascular disease in a patient with systemic lupus erythematosus is a marker of central nervous system and renal disease, with increased mortality in such patients [11–13]. The patient’s visual acuities improved to 20/80 right eye and 20/40 left eye, and after seven sessions of plasmaphoresis and intravenous cyclophosphamide her therapy was transitioned to 20 mg of methotrexate subcutaneous once weekly along with low dose daily oral prednisone. The patient’s more recent visual acuities were 20/125 OD and 20/25 OS, with her being maintained on methotrexate and supplemental systemic corticosteroids. Lupus “flares”, with compliment consumption and immune complex production have occurred three times during her 10 years of follow-up care, all responding to brief increases in systemic corticosteroid dosing.

Polyarteritis nodosa

Polyarteritis nodosa, a well-recognized highly lethal systemic vasculitic disease, may have as its first manifestation
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leading the patient to seek medical care, ocular inflammation. Scleritis, peripheral ulcerative keratitis, and retinal vasculitis are the predominant ocular inflammatory manifestations of this disease, which has a death rate of 85% if untreated [14], a death rate of 50% if treated with corticosteroids only [15], and a death rate of only 5% if treated with cyclophosphamide and systemic corticosteroids with tapering of the corticosteroids [16,17]. A development of peripheral ulcerative keratitis or scleritis or retinal vasculitis in a patient with already diagnosed polyarteritis nodosa, on therapy, is indicative of a need for more vigorous therapy regardless of other findings, a phenomenon quite similar to that described in the patients with rheumatoid arthritis or with systemic lupus erythematosus.

Case example

The following case example demonstrates, for a different disorder, the eye as the initial manifestation of an as yet undiagnosed potentially lethal systemic disease. The patient, a 45-year-old male, developed sectoral scleritis and peripheral ulcerative keratitis, right eye. (Fig. 6) This was treated with topical and systemic corticosteroids, and through time the problem worsened, with progression of the PUK. (Fig. 7) Extensive evaluations failed to detect any extra-ocular abnormality. Nine months after the onset of the eye problem, a small patch of nodular dermatitis developed

Figure 6. Peripheral ulcerative keratitis with adjacent scleritis. The eye is painful and tender to the touch. It took many months before the underlying diagnosis of granulomatosis with polyangiitis (Wegener’s) was established and effective therapy implemented.

Figure 7. Same patient as shown in Fig. 6. Note the extension of the peripheral ulcerative keratitis.

Figure 8. Same patient as shown in Figs. 6 and 7. The necrotizing lesion on the skin of the cheek has now evolved, still without a clear underlying diagnosis.
in the right cheek (Fig. 8). The patient neglected this new lesion, and over the next 2 months the problem worsened (Fig. 9), and the inflammatory disease in the patient’s right eye also worsened, with necrotizing scleritis development, and progression of the peripheral ulcerative keratitis to encompass 270 degrees of the peripheral cornea. Scleral biopsy disclosed the presence of vasculitis, (Fig. 10) accompanied by numerous multinucleated giant cells (Fig. 11). Chest X-ray, which had previously been perfectly normal 9 months earlier, now showed nodular densities in both lungs (Fig. 12). Sinus X-rays, which had previously been normal, now showed opacification of the left maxillary sinus (Fig. 13).

The diagnosis of granulomatosis with polyangiitis (Wegener’s) was made, and the patient was treated with cyclophosphamide, which resolved the ocular inflammation as well as the sinus and chest pathology (Fig. 14). This case preceded the discovery of antineuclear cytoplasmic antibodies in patients with granulomatosis with polyangiitis, and, conceivably, had that test been available at the time I cared for this gentleman, the diagnosis of the underlying systemic disease could have been made earlier. However, it is to be remembered that 30% of patients with granulomatosis with polyangiitis are ANCA negative until late in the course of the disease, emphasizing the importance of the ophthalmologist as positioned remembering his or her clinical medicine diagnostic skills. More recent work with this disease (GPA) has disclosed, through masked controlled trials, that rituximab is equally efficacious in inducing remission of the disease when compared to cyclophosphamide [18].

**Relapsing polychondritis**

Relapsing polychondritis may have ocular manifestations, but very often eye involvement is not part of the clinical

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**Figure 9.** Worsening of the ocular lesion in this patient in whom diagnosis was eventually made by histopathology, i.e., granulomatosis with polyangiitis (Wegener’s).

**Figure 10.** Histopathology of biopsied ocular inflammation in previous patient. Note the microangiopathy of lymphocytes clustering around blood vessels.

**Figure 11.** Same patient, same tissue, different field. Note the array of multinucleated giant cells.

**Figure 12.** Chest X-ray in the same patient diagnosed with granulomatosis with polyangiitis (Wegener’s). The chest X-ray 6 months earlier had been perfectly normal.
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Figure 13. Sinus X-ray, same patient. As in Fig. 12, the sinus X-ray 6 months earlier had been perfectly normal. Note now, however, the opacification of the right macullary sinus, typical of a patient with sinus pathology from granulomatosis with polyangiitis (Wegener’s).

picture initially. The patient may have chondritis involving ear (Fig. 15) or nose, and in such instances the employment of Dapsone with an oral non-steroidal anti-inflammatory drug and low dose corticosteroid therapy is typically sufficient to induce remission. However, scleritis and/or peripheral ulcerative keratitis may eventually develop in patients with relapsing polychondritis, and in such instances a need for a change in therapy is evident. Specifically, the employment of cyclophosphamide can be not only sight saving but also life saving. Tracheal involvement with collapse of tracheal cartilage is usually avoidable if one increases the vigor of therapy early in the course of the disease (Fig. 16).

In conclusion, rheumatologists would be well advised to be guided by the ophthalmologist regarding the need for

Figure 14. Same patient as in the previous two figures, 6 months into therapy with systemic cyclophosphamide. Note the complete resolution of the ocular inflammation, and the healing of the peripheral ulcerative keratitis. The patient’s visual acuity is 20/20.

Figure 15. Auricular involvement in a patient with relapsing polychondritis. This patient had necrotizing scleritis and peripheral ulcerative keratitis for more than 1 year prior to the evolution of the cartilage pathology in the ear.

Figure 16. An additional patient with relapsing polychondritis. Note, in addition to the scleritis and the saddle nose deformity from cartilage damage to the nose, the fact that the patient has a tracheostomy. This was avoidable, had the doctors involved in her care been aware of the clinical significance of the onset of scleritis in a patient with relapsing polychondritis. More aggressive therapy 6 months earlier would have obviated the need for the tracheostomy.
increased therapeutic vigor when an inflammatory ocular lesion exists. And ophthalmologists would be well advised to
guide the rheumatologist regarding the need for increased
therapeutic vigor when inflammatory ocular lesions exist
by providing to him or her reprints of the vast literature
in ophthalmic journals, which exist on this matter. This
publication and its references are intended to aid in this
effort.

Disclosure of interest
The author declares that he has no conflict of interest con-
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