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Scleritis and rheumatoid arthritis

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Holthouse (1893) presented an unusual case of ulceration of the conjunctiva and sclera in a patient who also suffered from rheumatoid arthritis and described the typical histology of the condition. Nevertheless, van der Hoeve (1934), in the first description of scleromalacia perforans, which occurred in three cases in association with a polyarthritis, regarded the condition as a primary degeneration of the sclera. Thereafter, however, the association of scleritis with rheumatoid arthritis and other connective tissue diseases has been well established (Watson and Lobascher, 1965; Sevel, 1967; Lyne and Pitkeathley, 1968) and is regarded as being due to the development of rheumatoid nodules within the sclera (Verhoeff and King, 1938; Edström and Osterlind, 1948; Anderson and Margolis, 1952; Sevel, 1965; Smiley and Bywaters, 1967; Watson, Hayreh, and Awdry, 1968). The prevalence of scleritis in rheumatoid arthritis is not well established and has been thought to be a rare complication (Smiley and Bywaters, 1967). Smith (1957) found one case of scleral involvement recorded in a retrospective study of the records of 465 rheumatoid patients, and by personal communication, Sevel (1965) estimated the prevalence to be one in three thousand cases.

This study has been directed at determining the prevalence and nature of scleritis in rheumatoid arthritis and the place of this complication in the natural history of rheumatoid disease.

Method

A careful examination of the eyes, with particular attention to scleral inflammation and thinning, was performed in 142 consecutive in-patients and out-patients with definite or classical rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) together with the same number of controls (hospital in-patients with non-inflammatory orthopaedic conditions matched for age and sex). A further five rheumatoid patients specially referred because they were known to have scleritis were included separately. Slit-lamp examinations of the eyes were performed in every positive case. Scleritis and episcleritis were differentiated according to the criteria summarized in Table I, which are based on the descriptions of Watson and others (1968). Inactive scleritis was diagnosed only when there was a past history of scleral inflammation, a definite diagnosis of scleritis had been made at that time, and marked scleral thinning had subsequently developed.

Table I *Differentiation between scleritis and episcleritis*

Characteristics	*Episcleritis*	*Scleritis*
Definition	Inflammation of the episcleral (subconjunctival) tissues	Inflammation of the scleral coat of the eye
Course	Usually fairly acute in onset and resolves within 3 weeks	Acute or slow in onset; may resolve in a few weeks or last 1 to 2 years
Symptoms	Discomfort only, vision not affected	May cause severe pain and general malaise, vision may be blurred
Types	Simple or nodular	Simple, diffuse, nodular, or necrotizing
Signs	Conjunctival and superficial episcleral vascular plexuses affected, nodules are superficial and can be moved Cornea not affected	Deep episcleral vascular plexus affected, superficial vessels may also be affected, nodules are deep and fixed to the sclera Cornea may be affected (sclerokeratitis)
Outcome	No residual physical signs	Followed by scleral thinning; may have serious complications, including perforation

A detailed study was made of both the joint and systemic manifestations of the rheumatoid disease and comparisons were drawn between those rheumatoid patients who developed scleritis and those who did not.

Whenever possible, follow-up assessments were performed to determine the course of the eye disease and its relationship to activity of the arthritis.

Results (Tables II to IV)

Evidence of scleritis was found in nine of the 142 rheumatoid patients who were screened but in none of the controls, a highly significant association ($\chi^2 = 7 \cdot 34$; $P < 0 \cdot 01$). Of these nine, six showed active and three inactive scleritis, and of the five added to the series all showed active scleritis.

Both eyes were affected in ten of the fourteen patients with scleritis. The superior quadrant of the eye was involved most frequently and the inferior quadrant least often (Fig. 1), but the differences were not statistically significant. All patients with active scleritis showed diffuse inflammation in the sclera, but four of these also had scleral nodules.

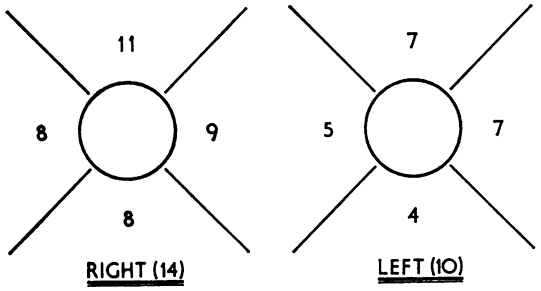


FIG. 1 *Sites of scleral inflammation in fourteen rheumatoid patients*

The mean age and length of history of arthritis were similar in the patients with and without scleritis. The erythrocyte sedimentation rate was higher in the former group but the difference was of borderline statistical significance. There was a significant association between scleritis and rheumatoid nodules and, in particular, the four patients with scleral nodules all had rheumatoid nodules. There was an increased frequency of pericarditis/pleurisy among the scleritics, the two patients both having suffered pericarditis and one also pleurisy, eventually undergoing pericardectomy and pleurectomy. Evidence of arteritis was found in ten of the fourteen scleritic patients and in only sixteen of the remaining rheumatoid patients, a highly significant association. Among these ten, four showed nail-fold lesions with microvasculitis, five arteritic skin ulceration, and two peripheral neuropathy. All systemic complications of rheumatoid arthritis taken together showed a highly significant correlation with scleritis. Although all the fourteen scleritics had positive Waaler-Rose tests and radiological erosions, these were not significantly more frequent than in the non-scleritics. Both groups of patients were receiving systemic steroids in similar dosages.

Four of the patients have observed that attacks of inflammation in the eyes coincide with exacerbations of arthritis but, in general, the eye symptoms were mild and one patient was unaware of the inflammation in the sclera. In one patient the scleritis preceded the onset of rheumatoid arthritis by 4 years, and with the onset of joint symptoms the eye disease became worse.

Follow-up examinations were performed in ten patients, at periods varying from 3 to 18 months. In two patients the eyes remained relatively unchanged. One of these had shown only thinning of the sclera with no active scleritis, but in the other inflammatory changes and nodules persisted as

Table II *Incidence of scleritis*

Series	*Nos. studied*		*Scleritis*		*Sex*	
	Male	*Female*	*Active*	*Inactive*	*Male*	*Female*
Controls	27	115	0	0	0	0
Rheumatoid arthritis	27	115	6	3	3	6
Special referrals	3	2	5	0	3	2

Table III *Age, duration, and sedimentation rate*

Scleritis	*Present*	*Absent*	*t*	*Significance*
Mean age (yrs)	$56 \cdot 5 \pm 10 \cdot 7$	$58 \cdot 0 \pm 11 \cdot 2$	0·48	$P < 0 \cdot 7$
Lenth of history of RA (yrs)	$13 \cdot 0 \pm 11 \cdot 1$	$11 \cdot 9 \pm 10 \cdot 1$	0·38	$P < 0 \cdot 8$
Erythrocyte sedimentation rate (mm./hr)	$63 \cdot 4 \pm 28 \cdot 1$	$49 \cdot 5 \pm 29 \cdot 7$	1·68	$P < 0 \cdot 1$

Table IV *Scleritis related to other signs and symptoms*

Scleritis		*Present*	*Absent*	χ^2	*Significance*
Rheumatoid nodules	Present	10	34	10·62	P <0·01
	Absent	4	99		
Pericarditis/Pleurisy	Present	2	1	5·80	P <0·05
	Absent	12	132		
Arteritis	Present	10	16	26·76	P <0·001
	Absent	4	117		
Systemic complications	Present	11	18	29·86	P <0·001
	Absent	3	115		
Waaler-Rose titre ⩾1·32		14	109	1·40	P <0·3
<1·32		0	20		
Erosions	Present	14	99	2·19	P <0·2
	Absent	0	25		
Receiving systemic steriods			72	0·20	P <0·7
Not receiving systemic steroids			61		

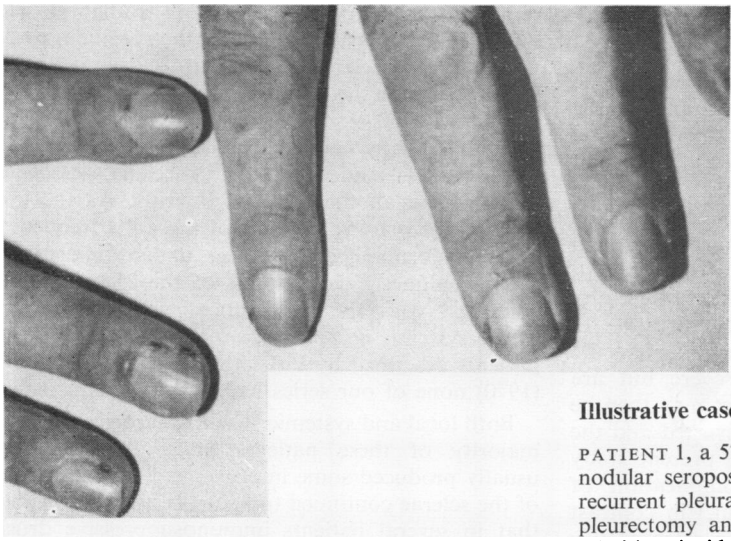


FIG. 8 *Patient* 3. *Microvasculitis of fingers*

before. In the remaining eight patients the eyes showed varying degrees of improvement. In three patients all signs of active scleritis disappeared and the sclerae showed only slight thinning. It was remarkable that one of these patients still continued to have active arteritis elsewhere. The remaining five patients showed varying amounts of residual inflammation and thinning in the sclera. All these patients were treated with corticosteroid eyedrops and five of seven showed improvement with systemic corticosteroids. Five of these seven were also receiving immunosuppressive drugs and it was noticed, particularly in two, that improvement in eye symptoms occurred only with the addition of these agents.

Illustrative cases (see colour plate, overleaf)

PATIENT 1, a 57-year-old man with a 26-year history of nodular seropositive rheumatoid arthritis, had suffered recurrent pleural and pericardial effusions necessitating pleurectomy and pericardectomy. The first episode of scleritis coincided with the first attack of pleurisy 4 years previously and recurrences of chest pain and eye symptoms coincided thereafter. Both eyes showed areas of active scleritis and scleral atrophy from previous attacks (Fig. 2). He was already receiving systemic prednisone (10 mg. daily) and betamethasone eye drops, but, with the addition of azathioprine 150 mg. daily, the activity of the arthritis decreased and signs of active scleral inflammation disappeared leaving only thinning (Fig. 3).

PATIENT 2, a 49-year-old woman with a 6-year history of nodular seropositive rheumatoid arthritis, was in hospital when she developed acute scleritis of the right eye with marked scleral injection and oedema in the superior sclera (Fig. 4). This was accompanied by considerable pain. She was already receiving prednisone and azathioprine but, 2 weeks after an increase in dose of the

latter, the eye inflammation was considerably reduced (Fig. 5). One year later only scleral thinning was observed (Fig. 6).

PATIENT 3, a 58-year-old woman with nodular seropositive erosive rheumatoid arthritis, was receiving adrenocorticotrophic hormone and had normal eyes when first seen, but 1 week later she simultaneously developed acute scleritis of both eyes (Fig. 7) and multiple microvasculitis of the fingers (Fig. 8, previous page).

The corticotrophin therapy was increased and with betamethasone eye drops the eye symptoms gradually improved and the vascular lesions healed. 6 months later there was still some active inflammation as well as scleral thinning (Fig. 9).

PATIENT 4, a 69-year-old man with nodular seropositive rheumatoid arthritis with evidence of microvasculitis of the fingers, was unaware of any eye symptoms. He showed both active inflammation and thinning in the sclera and also an area of scarring of the margin of the cornea typical of resolved scleral keratitis (Fig. 10).

Discussion

Scleritis is a well-defined inflammatory change in the scleral coat of the eye. Nodular, diffuse, and necrotizing types of scleritis have been described (Watson and others, 1968), but in practice we have found these distinctions difficult as many cases show two or even all three of these features. Episcleritis, on the other hand, is a more superficial inflammation deep to the conjunctiva which may be difficult to distinguish from conjunctivitis. It may well not be true entity and we found no cases in the present series.

Scleritis often presents as a recurrent subacute inflammation. Symptoms may be severe but are occasionally minimal and the changes may then be easily missed if the eyelids are not everted and the sclerae specifically examined. In the present study scleritis was a not uncommon complication of rheumatoid arthritis (over 6 per cent.) in contrast to its comparitive rarity in previous retrospective surveys.

Previous reports of scleritis (Sevel, 1965, Smiley and Bywaters, 1967; Lyne and Pitkeathly, 1968) have emphasized that the superior sclera is most commonly affected. In the present study the superior sclera was most frequently involved. Perhaps we should think of the anterior part of the eye as a joint with scleritis analogous to rheumatoid joint disease. Movement of the eyelid is most marked over the superior quadrants so that this type of inflammation is most frequent here.

The pathology of the nodular scleritis has been described many times (Holthouse, 1893; Edström and Osterlind, 1948; Sevel, 1965; Smiley and Bywaters, 1967). It is that of a typical rheumatoid nodule with a surrounding inflammatory response. Inflammation may spread to the episclera, choroid, ciliary body, and retina, producing secondary complications such as choroiditis, choroidoretinitis, retinal detachment, keratitis, cyclitis, episcleritis, cataract, secondary glaucoma, and perforation (Sevel, 1965). Fortunately none of the patients in this series developed these features although one has such gross scleral atrophy that perforation may eventually occur.

Only limited experimental work on the pathogenesis of scleritis has been performed. Sevel (1968) showed that necrosis did not occur in an isolated segment of sclera or at the sites of surface diathermy, retinal detachment, and areas of irradiation. He interpreted this as showing that the specific type of necrosis of the sclera is not due to ischaemia alone, but is related to the basic disease. The present study emphasizes the association of scleritis with rheumatoid arthritis, and particularly with systemic complications and vasculitis. The analyses were drawn using all the cases of scleritis. As the eye disease was inactive in some of these the frequency of systemic manifestations was underestimated by this technique. Exacerbations of the scleritis often coincided with the appearance and exacerbation of the systemic complications. In contrast with the patients described by Pitkeathly, Howitt, and Lyne (1970) none of our series had aortic incompetence.

Both local and systemic steroids were given to the majority of these patients and, although they usually produced some improvement, inflammation of the sclerae continued to recur. It was remarkable that in several patients immunosuppressive drugs produced a dramatic improvement in the scleral inflammation, and in two cases complete disappearance of all signs of activity coincided with administration of these drugs.

FIG. 2 *Patient* 1. *Right eye, active scleritis and scleral thinning*

FIG. 3 *Patient* 1. *Right eye, complete resolution of active scleritis leaving scleral thinning following immunosuppressive therapy*

FIG. 4 *Patient* 2. *Right eye, acute inflammation and oedema in superior sclera*

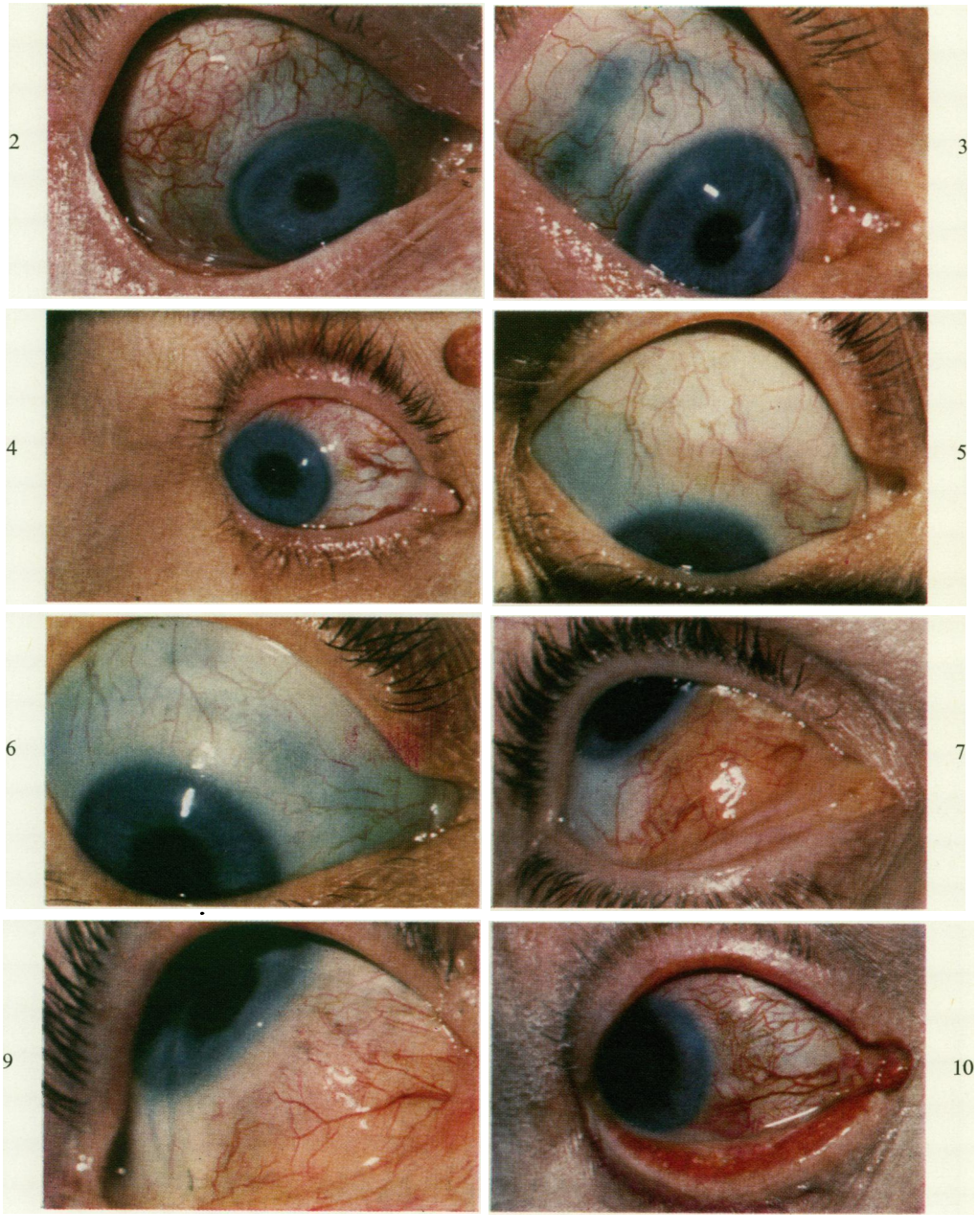
FIG. 5 *Patient* 2, *Right eye* 2 *weeks later, considerable resolution of the acute inflammation*

FIG. 6 *Patient* 2. *Right eye* 1 *year later, scleral thinning only*

FIG. 7 *Patient* 3. *Right eye, acute scleritis in medial and inferior quadrants*

FIG. 9 *Patient* 3. *Right eye* 6 *months later, slight inflammation and scleral thinning*

FIG. 10 *Patient* 4. *Right eye, acute scleritis, with some opacity of the supero-medial edge of the cornea typical of resolved scleral keratitis.*



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Summary

The sclerae of 142 patients with rheumatoid arthritis and of the same number of controls were examined. No cases of episcleritis were found in either group. Evidence of scleritis was present in nine of the rheumatoid patients but in none of the controls, a significant association. A further five patients specially referred because of known scleritis were also examined. The disease was usually bilateral and was significantly associated with rheumatoid nodules, arteries, pericarditis/pleurisy, and systemic complications of rheumatoid arthritis as a whole.

Exacerbations of the scleritis often coincided with activity of the rheumatoid disease and of complications, but in several cases the disease was relatively mild with minimal symptoms and a protracted course. At follow-up, eight of ten cases showed lessening of the inflammation with development of scleral thinning. Most had responded to systemic and local corticosteroids but in two improvement occurred only after the addition of immunosuppressive therapy.

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