Ocular Characteristics and Disease Associations in Scleritis-Associated Peripheral Keratopathy

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**Objectives:** To evaluate ocular characteristics and systemic disease associations in patients with scleritis-associated peripheral keratopathy and its different patterns, and to assess any ocular or systemic prognostic significance of the presence of the types of peripheral keratopathy in patients with scleritis.

**Design:** Review of 125 patients with scleritis alone and 47 patients with scleritis-associated peripheral keratopathy; review of patients with scleritis and the different patterns of peripheral keratopathy: peripheral corneal thinning, stromal keratitis, and peripheral ulcerative keratitis (PUK); review of ocular and systemic outcomes comparisons between patients with scleritis with and without peripheral keratopathy.

**Results:** Patients with peripheral keratopathy had more necrotizing scleritis (57%, \(P < .001\)), decrease in vision (81%, \(P < .001\)), anterior uveitis (62%, \(P < .002\)), impending corneal perforation (62%, \(P < .001\)), and potentially lethal specific-disease association (87%, \(P < .001\)) than did patients with scleritis alone. Patients with PUK had the worst ocular and systemic outcomes. Of the 24 patients with PUK, 16 (67%) had necrotizing scleritis (\(P = .02\)), virtually all had a potentially lethal systemic disease (\(P = .02\)), and all had impending corneal perforation (\(P < .001\)).

**Conclusion:** The detection of peripheral keratopathy, and especially PUK, in a patient with scleritis indicates a poor ocular and systemic prognosis.

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**RESULTS**

A total of 47 patients (27.3%; 65 eyes) with scleritis had an associated peripheral keratopathy; 12 patients (16 eyes) had peripheral corneal thinning, 11 patients (15 eyes) had stromal keratitis, and 24 patients (34 eyes) had PUK.

Patients with scleritis-associated keratopathy (47 patients, 65 eyes) were compared with patients with scleritis alone (125 patients, 166 eyes) (Table 1). Eleven patients (18 eyes) with keratopathy had diffuse scleritis, 9 patients (11 eyes) had nodular scleritis, 26 patients (35 eyes) had necrotizing scleritis, and 1 patient (1 eye) had both anterior (diffuse) and posterior scleritis. Comparisons of types of scleritis between patients with and without peripheral keratopathy showed that diffuse...
SUBJECTS AND METHODS

We reviewed the records of 172 consecutive patients (231 eyes) with scleritis seen in the Ocular Immunology and Uveitis Service of the Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, during an 11-year period and divided them into 2 categories: those with and those without peripheral keratopathy. Patients with scleritis-associated peripheral keratopathy were further divided into subgroups depending on the pattern: peripheral corneal thinning, stromal keratitis, and PUK. The 3 patterns of scleritis-associated peripheral keratopathy were defined as follows:

- In peripheral corneal thinning, the periphery of the cornea (within 2-3 mm of the limbal margin) becomes grayish and about one-third thinner in 1 or more areas. The epithelium remains intact throughout the thinning process.
- In stromal keratitis, isolated or multiple white or gray nummular opacities composed of leukocytes appear within the corneal stroma, and, unless successfully treated, expand slowly toward the periphery and/or center of the cornea. The epithelium is intact.
- Finally, PUK is a peripheral corneal ulcer with epithelial defects, stromal infiltration, and stromal degradation. The ulcer has a well-defined border on its limbal and corneal edges.

Patient data, including age, sex, type of peripheral keratopathy, type of scleritis, bilaterality of peripheral keratopathy, and previous ocular surgery, were analyzed. Scleritis was characterized as anterior or posterior, according to the classification of Watson and Hayreh; anterior scleritis included the diffuse, nodular, necrotizing, and scleromalacia perforans types. For the purpose of this study, scleritis-associated peripheral keratopathy after ocular surgery was defined as scleral inflammation and peripheral keratopathy appearing in the exact area of the previous surgical procedure.

Ocular manifestations, including permanent loss of best-corrected visual acuity, anterior uveitis, and impending corneal perforation, were analyzed. Decrease in visual acuity was defined as loss of vision of 2 or more Snellen lines at the end of the follow-up period or visual acuity of 20/80 or worse at presentation related to the inflammatory disease process. Anterior uveitis was diagnosed based on the detection of inflammatory cells in the anterior chamber with or without synechiae or keratic precipitates. Impending corneal perforation was defined as progressive destruction of the peripheral cornea, leaving only some layers of deep stroma and/or Descemet membrane.

We studied specific disease association as a result of compatible history, review of systems, laboratory, and biopsy data. For the purpose of this study we grouped interrelated disorders under the term spondyloarthropathy; those disorders include ankylosing spondylitis, Reiter syndrome, psoriatic arthritis, and arthritis and inflammatory bowel disease (Crohn disease and ulcerative colitis).

Data were analyzed with a customized database software program, and comparisons were made between patients with scleritis-associated peripheral keratopathy and patients with scleritis alone. A multifactorial analysis of variance was performed for all variables except age (Mann-Whitney test). Relative risk analysis between patients with scleritis with and without peripheral keratopathy was conducted for all variables except age. Comparisons were also made among scleritis patients with different patterns of peripheral keratopathy (peripheral corneal thinning, stromal keratitis, and PUK). Statistical analysis was performed with the χ² test for 3 variables; specific analysis between groups of 2 patterns was conducted with the χ² test for 2 variables with a Bonferroni adjustment.

Scleritis was significantly more frequent in patients without peripheral keratopathy (P < .001), and necrotizing scleritis was significantly more frequent in patients with peripheral keratopathy (P < .001). Nodular scleritis did not differ significantly when compared in patients with scleritis with and without peripheral keratopathy.

Patients with scleritis-associated keratopathy (mean age, 62.53 years; range, 15-85 years) were older than patients without peripheral keratopathy (mean age, 48.47 years; range, 11-87 years) (P < .001). Twenty-seven patients (57.4%) with keratopathy were women, and 20 (42.6%) were men. The predominance of women did not differ significantly when patients with scleritis with and without keratopathy were compared. Scleritis was bilateral in 18 patients (38.3%) with peripheral keratopathy and in 41 patients (32.8%) without peripheral keratopathy. This difference was not statistically significant. Previous ocular surgery was detected in 18 patients (38.3%) with scleritis-associated peripheral keratopathy and in 10 patients with scleritis alone (8%) (P < .001). The mean interval between ocular surgery and onset of scleritis was 6.62 months (range, 1-14 months) and 11.2 months (range, 1-28 months), respectively. Previous ocular surgical procedures included cataract extractions in all patients with peripheral keratopathy and in all but 2 patients with scleritis alone; those 2 patients developed scleritis following strabismus and retinal detachment procedures, respectively.

In patients with peripheral keratopathy, 38 (80.9%) had decrease in vision, 29 (61.7%) had anterior uveitis, and 29 (61.7%) had impending corneal perforation. Comparisons of these conditions between patients with keratopathy and those with scleritis alone showed that decrease in vision, anterior uveitis, and impending corneal perforation were found more frequently in patients with peripheral keratopathy (P < .001, P = .002, and P < .001, respectively).

An associated disease was found in 41 patients (87.2%) with peripheral keratopathy and in 57 patients (45.6%) with scleritis alone (P < .001). Specific associated diseases in patients with scleritis with and without peripheral keratopathy included connective tissue or vasculitic diseases in 34 patients (72.3%) and 52 patients (41.6%), respectively, and infectious diseases in 7 patients (14.9%) and 5 patients (4%), respectively (Table 2). Rheumatoid arthritis, Wegener granulomatosis, and infectious diseases were found more frequently in patients with peripheral keratopathy than in...
patients with scleritis without peripheral keratopathy (P < .001, P < .001, and P = .01, respectively).

Relative risk analyses showed that, compared with patients with scleritis alone, patients with peripheral keratopathy were 5.3 times more likely to have necrotizing disease and 4.8 times more likely to have had previous ocular surgery. The relative risks for complications in patients with peripheral keratopathy were 3.9 for decrease in best-corrected visual acuity, 1.7 for anterior uveitis, and 1.9 for associated diseases (Table 3). Furthermore, patients with peripheral keratopathy were 3.4 times more likely to also have Wegener granulomatosis and 3.7 times more likely to have an infectious disease.

Comparisons among the different patterns of peripheral keratopathy with respect to types of scleritis and previous ocular surgery (Table 4 and Table 5) showed that PUK was more frequently associated with necrotizing scleritis (16 patients, 66.7%) and previous ocular surgery (14 patients, 58.3%) than was stromal keratitis (7 patients, 63.4%) (P = .02 and P = .03, respectively).

Comparisons among the different patterns of peripheral keratopathy with respect to ocular manifestations (Table 4 and Table 5) did not show statistically significant differences for decrease in vision and anterior uveitis. However, PUK was more frequently associated with impending corneal perforation (24 patients, 100%) than other patterns (3 patients, 25%) or stromal keratitis (2 patients, 18%) (P < .001 and P < .001, respectively).

Comparisons among different patterns of peripheral keratopathy with respect to specific disease associations (Table 4 and Table 5) showed that PUK was more frequently correlated with an associated disease (24 patients, 100%) than was stromal keratitis (7 patients, 63.4%) (P = .02). Different patterns of peripheral keratopathy did not differ significantly with respect to specific associated diseases (Table 6).
The results of this study provide insight into the severity of scleritis-associated peripheral keratopathy and its different patterns. The detection of peripheral keratopathy in a patient with scleritis should be regarded as a grave ocular sign because scleritis patients with peripheral keratopathy more often had necrotizing scleritis, decrease in vision, anterior uveitis, and impending corneal perforation. In addition, it is interesting to compare scleritis-associated peripheral keratopathy at different tertiary referral centers. Our proportion of scleritis patients with peripheral keratopathy (65 of 231 eyes, 28%) is similar to the proportion reported in a large retrospective study performed in 1976 by Watson and Hayreh at Moorfields Eye Hospital, London, England (88 of 301 eyes, 29%). However, the peripheral keratopathy population from our service showed a higher proportion of eyes with necrotizing scleritis (35 of 48 eyes, 73%) and a lower proportion of eyes with diffuse scleritis (18 of 197 eyes, 17%) and nodular scleritis (11 of 50 eyes, 22%) than the population reported by Watson and Hayreh (necrotizing scleritis, 59% of eyes; diffuse scleritis, 23%; and nodular scleritis, 26%).

The detection of peripheral keratopathy in a patient with scleritis is also a warning sign of increased likelihood of an associated disease. In this study, scleritis patients with peripheral keratopathy more often had an associated disease than patients with scleritis alone (87% vs 46%). Rheumatoid arthritis, Wegener granulomatosis, and infectious diseases were the most common associated diseases.

Several distinctive patterns of peripheral keratopathy are found in patients with scleritis: peripheral corneal thinning, stromal keratitis, and PUK. In our experience, all 3 patterns may cause decrease in vision and may be associated with anterior uveitis. Studies with anterior segment fluorescein angiography showed that corneal thinning, stromal keratitis, and PUK in patients with scleritis had varying degrees of vaso-occlusive changes in the arterial, venous, or capillary circulations of the episcleral and conjunctival vasculature. In some instances, this vascular shutdown may lead to catabolic resorption of the stromal tissue. The larger the area of vaso-occlusion, the greater the degree of corneal and scleral destruction. Therefore, the vaso-occlusive changes of peripheral corneal thinning or stromal keratitis are less extensive than the ones present in PUK. Furthermore, the area of vaso-occlusion is larger if areas of peripheral corneal thinning or stromal keratitis undergo impending corneal perforation. In our experience, impending corneal perforation was present in patients with all 3 patterns of peripheral keratopathy, but it was found most frequently in patients with PUK.

Histopathologic studies on conjunctival, episcleral, and scleral biopsies from patients with PUK and necrotizing scleritis showed that most had an inflammatory microangiopathy of the episcleral and conjunctival vasculature. All patients with PUK had an associated disease, including systemic vasculitis diseases and infectious diseases. The inflammatory microangiopathy in scleritis patients with PUK may be caused by the extension of a systemic vasculitis process, a bacterial or viral infection, or a local immune response to these organisms.

Inflammatory microangiopathy of the episcleral and conjunctival vasculature may be triggered by trauma such as ocular surgery in predisposed patients with systemic vasculitic disease. This may result in scleral and/or corneal destruction. In this study, the pattern of peripheral keratopathy most frequently found after ocular surgery such as cataract extraction was PUK. All patients with

<table>
<thead>
<tr>
<th>Condition</th>
<th>Peripheral Corneal Thinning (n = 12)</th>
<th>Stromal Keratitis (n = 11)</th>
<th>Peripheral Ulcerative Keratitis (n = 24)</th>
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<tbody>
<tr>
<td>Scleritis</td>
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<td></td>
<td></td>
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<td>Anterior</td>
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<td>16</td>
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<tr>
<td>Impending corneal perforation</td>
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<tr>
<td>Associated disease</td>
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<td>7</td>
<td>24</td>
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</tbody>
</table>

*Groups compared with a χ² test for 3 variables. NA indicates not applicable; ellipses, nonsignificant findings (P> .05).
† Condition not included in the χ² test because of the small number of patients.
‡ All patients with posterior and anterior scleritis had anterior diffuse scleritis.

<table>
<thead>
<tr>
<th>Condition, P Value</th>
<th>Diffuse Scleritis</th>
<th>Necrotizing Scleritis</th>
<th>Previous Ocular Surgery</th>
<th>Impending Corneal Perforation</th>
<th>Associated Disease</th>
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<tr>
<td>Peripheral corneal thinning vs stromal keratitis</td>
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<td>Peripheral corneal thinning vs peripheral ulcerative keratitis</td>
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<td>Stromal keratitis vs peripheral ulcerative keratitis</td>
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*Groups compared with a χ² test for 2 variables with a Bonferroni adjustment. Ellipses indicate nonsignificant findings (P> .05).
PUK had an underlying vasculitic disease. Immune complex–mediated vasculitic damage following the surgical trauma may underlie the pathogenesis.9,10

The findings presented here are clinically relevant and provide important advice for practicing ophthalmologists:

- Look for corneal involvement in every follow-up visit of a patient with scleritis. Scleritis patients with peripheral keratopathy must be followed especially closely because they are more likely to have necrotizing scleritis, decrease in vision, anterior uveitis, and impending corneal perforation than patients with scleritis alone.

- Search for an underlying disease in all scleritis patients. Scleritis patients with peripheral keratopathy are especially likely to have an associated disease, the most common being rheumatoid arthritis, Wegener granulomatosis, and infectious diseases.

- Distinguish the different patterns of scleritis-associated peripheral keratopathy. Although scleritis patients with any type of peripheral keratopathy may have ocular complications, such as decrease in vision, anterior uveitis, and impending corneal perforation, scleritis patients with PUK have the worst ocular prognosis because they have the highest risk of developing impending corneal perforation. Furthermore, scleritis patients with PUK more frequently have potentially lethal underlying diseases.

- Be aware that surgical trauma may trigger inflammatory microangiopathy (episcleral and conjunctival vasculature) in a predisposed patient with a systemic vasculitic disease, resulting in scleritis-associated peripheral keratopathy. Investigate such patients aggressively to identify this potentially lethal disease while it is still amenable to successful treatment.

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REFERENCES


A look at the past...

Druault (Paris): On the Pathology of Quinine Amaurosis

Experiments on dogs showed that quinine amaurosis was due to the toxic action of the quinine upon the ganglion cells of the retina, which degenerate, rather than to the ischaemia caused by the spasm of the vessels.