Non-Infectious Scleritis and Systemic Collagen Vascular Disease Association

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ABSTRACT

Objective: To evaluate the differences between scleritis in association with a systemic collagen vascular disease and idiopathic scleritis and to describe the clinical characteristics of patients presenting with non-infectious scleritis.

Methods: A retrospective cohort study of 95 patients who presented with non-infectious scleritis was conducted. A comparison of the clinical differences between patients who had an associated systemic collagen vascular disease and idiopathic scleritis was performed.

Results: Of the 95 patients (123 eyes), 72.6% was female with mean age of 47 years. Diffuse anterior scleritis was the most predominant type (57.9%). The first and the second most frequent complications were anterior uveitis and scleral thinning. Almost twenty percent of the patients had a systemic collagen vascular disease involvement; rheumatoid arthritis and non-specific anti-neutrophil cytoplasmic antibodies-related scleritis were the two most common (4.2% each). Most of the patients who had a concurrent systemic collagen vascular disease presented with diffuse anterior scleritis, but it was not statistically significant compared with the idiopathic group. The presence of scleral thinning during follow-up periods showed a statistically significant difference between the groups with and without systemic collagen vascular disease at p value 0.038.

Conclusion: Diffuse anterior scleritis was the most common type of scleritis found. Patients who had collagen vascular disease and scleritis commonly developed scleral thinning during follow up visits. Aggressive treatment for scleritis in immune-mediated systemic collagen vascular disease may be considered to prevent progressive scleral thinning.

Keywords: Scleritis; immune; rheumatology; inflammation (Siriraj Med J 2020; 72: 361-367)

INTRODUCTION

Scleritis is a considerably rare ocular disorder which can be characterized by an inflammation of the sclera. Most scleral inflammation is non-infectious in origin and is commonly associated with a systemic collagen vascular disease.[1,2] Previous studies established that approximately 25% to 50% of scleritis cases were associated with an underlying systemic inflammatory condition, including rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), seronegative spondyloarthropathies, and systemic lupus erythematosus.[2,3] RA and GPA were reported to have the highest associations.[2,4-6] Patients presenting with anterior scleritis typically complain of an eye pain with globe tenderness and progressive ocular redness, whereas patients presenting with posterior scleritis may present with a reduced vision without ocular pain.[4,7]

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Complications of scleritis can be mild, such as limited adjacent structural inflammation, or serious, such as scleral melting and perforation. The treatment decision between non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or immunomodulatory therapy (IMT) usually depends on disease severity and patient safety. The incidence of overall scleritis varies; in Northern California, it was reported as 3.4 cases per 100,000 person-years[8]; in a Pacific islander (Hawaiian) population, it was approximately 4.1 cases per 100,000 person-years[9]; and in the general population, it was claimed to be 6 cases per 100,000 person-years.[5] Scleritis occurs most frequently among women and the elderly.[10,11] We conducted this study to evaluate the clinical features of non-infectious scleritis in Thailand and the patterns of association of the scleritis with a systemic collagen vascular disease.

MATERIALS AND METHODS

This study was designed as a descriptive retrospective cohort study. A retrospective chart review of 95 patients with non-infectious scleritis presenting at Siriraj Hospital, Mahidol University, Thailand, between January 2013 and December 2015 was performed. The study was conducted in accordance with the declaration of Helsinki, and approved by the Ethics Committee of Siriraj Hospital, Mahidol University. Scleritis was defined as a presentation of edematous episcleral and scleral tissue with deep episcleral and scleral vessels engorgement. Application of 10% phenylephrine revealed no blanching of deep scleral vascular plexus. Scleritis classification was based on site of anatomical inflammation, which was anterior and posterior scleritis. For anterior scleritis, it could present as diffused scleral inflammation, localized nodular inflammation or necrotizing sclera. For posterior scleritis, fundus examination might reveal edematous optic disc and/or retinal striae or subretinal fluid. B-scan ultrasonography showed positivity of T-sign as a result of posterior scleral inflammation and adjacent swollen tenon. Patients with infectious related scleritis including bacteria, mycobacteria, spirochete, fungus, and parasite were excluded from the study. Mantoux test was done in some selected cases. Only patients who had been exposed to tuberculosis, was considered for the skin test. Treponemal and non-treponemal test was performed in most of the patients to rule out syphilitic infection. We documented the demographic data, the scleritis type (namely, diffuse anterior scleritis, nodular anterior scleritis, necrotizing scleritis with and without inflammation [also known as scleromalacia perforans], and posterior scleritis), and the associated systemic collagen vascular disease. The details documented were the ocular findings of a slit-lamp examination, the best-corrected visual acuity at the baseline visit and subsequent follow-ups, the number of recurrences, and the treatment (including any necessity for immunomodulatory therapy). As to the ocular complications, we collected details on associated peripheral ulcerative keratitis (PUK), anterior uveitis, scleral thinning, secondary ocular hypertension (OHT), vitritis, papillitis, cystoid macular edema (CME), and exudative retinal detachment (ERD). For scleral thinning, we normally documented it when sclera appeared blue on a slit lamp examination. Once non-infectious scleritis was suspected, we routinely perform laboratory investigations to evaluate possibility of systemic immune-related diseases. Not only basic laboratory investigations (complete blood count, liver and renal function test, urinalysis, chest radiogram) but also specific investigations such as rheumatoid factor, anti-citrullinated protein antibody, antinuclear antibodies, anticytoplasmic antibodies, erythrocyte sedimentation rate, C-reactive protein were performed. Some patients with symptoms specific to autoimmune diseases would be further investigated with some of the following tests: anti-double stranded DNA, anti-Smith, urine protein and urine protein to creatinine ratio, paranasal sinus radiogram, and may be sent for a rheumatologist consultation to evaluate cause of inflammation. For the subgroup analysis, we divided our patients into two groups: an idiopathic group, and a scleritis with associated systemic collagen vascular disease group. Patients with incomplete investigations were excluded from the subgroup analysis. For patients who had bilateral eye involvement, only the right eyes were used for analysis. The clinical features were described as descriptive statistics. Pearson's chi-squared test was used to compare categorical data, and Student's t-test was used to compare continuous data. To determine which variables were associated with systemic collagen vascular disease, a multivariate model was developed using variables significantly associated ($p < 0.1$) with systemic collagen vascular disease from univariate analysis. Variables found not to be significant or variables for which 95% confidence limits crossed the line of unity were excluded by backwards elimination, unless they improved the fit of the model. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Ethical approval for this study was provided by the Ethical Committee of Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 703/2015(EC2). Clinical Trials Registration: TCTR2017318001.

RESULTS

There were 95 non-infectious scleritis patients (123 eyes) during the study period; their mean age was 47 years (range: 12-88 years), and 69 patients were female (69/95,72.6%). Of the cohort, 67 presented with unilateral eye involvement (67/95, 70.5%), and 16 had recurrent inflammation (16/95, 16.8%). The numbers of the patients who had diffuse anterior scleritis, nodular anterior scleritis, posterior scleritis, and combined nodular anterior scleritis with posterior scleritis were 55/95 (57.9%), 29/95 (30.5%), 8/95 (8.4%), and 1/95 (1.1%), respectively. Scleritis type was not documented in 2 patients. None of our patients were diagnosed with necrotizing anterior scleritis. The most common associated finding reported in this study was anterior uveitis (39/95, 41.05%), with the second most common being scleral thinning (21/95, 22.11%). The other associated ocular findings were PUK (13/95, 13.7%); secondary OHT (13/95, 13.7%); papillitis (7, 7.37%); vitritis; CME; and ERD (the last three being found in equal numbers: 3/95, or 3.16% each). Through laboratory investigation, 18 patients had an associated systemic collagen vascular disease (18/95, 19%). RA and nonspecific antineutrophil cytoplasmic antibody (ANCA)-associated scleritis were the two most common systemic diseases (4/95, or 4.2% each), followed by systemic lupus erythematosus (3/95, 3.2%) and GPA (2/95, 2.1%). Unfortunately, 27.4% of our cases lacked thorough laboratory investigations to identify a possible associated systemic collagen vascular disease. From a subgroup analysis, after excluded patients with incomplete investigations, the mean age of the idiopathic group was 45.06 years, whereas it was 48.22 years for the scleritis with associated systemic collagen vascular disease group. Both groups were predominantly female, with 40/51 (78.4%) and 10/18 (55.6%) females, respectively. Interestingly, most of the patients in the scleritis with associated systemic collagen vascular disease group (24/27 eyes [88.9%]) presented with diffuse anterior scleritis; on the other hand, only about half of the patients in the idiopathic group (40/70 eyes [58.8%]) did so, which was statistically significant at p-value 0.054 in univariate analysis. The cause of inflammation of all eleven patients who presented with posterior scleritis was not found; thus, all of them were diagnosed with idiopathic posterior scleritis (16.2% versus 0%, p 0.026). As many as 9/27 eyes (33.3%) in the scleritis with associated systemic collagen vascular disease group had subsequent scleral thinning at their follow-up visits, compared to 8/70 eyes (11.4%) in the idiopathic group (p 0.038). No statistical significance was found for the other factors used to compare the differences between the two groups (namely, the best-corrected visual acuity on patients' first and last visits; laterality; the number of recurrences; scleral thinning on the first visit; and OHT, PUK, anterior uveitis, vitritis, CME, ERD, and papillitis on the first and follow-up visits); these are summarized in Table 1. Almost all of our patients received topical, regional, and/or systemic corticosteroids as their mainstay therapy. Some of them were treated with oral NSAIDs. Fifteen patients (29.4%) in the idiopathic group were treated with systemic IMT, whereas 10/18 patients (55.6%) in the scleritis with associated systemic collagen vascular disease group received IMT (p 0.047). Multivariate linear regression analysis between systemic collagen vascular disease association group and idiopathic group is shown in Table 2.

DISCUSSION

Although scleritis is scarcely seen in general ophthalmology practice, its serious complications and its possible association with a systemic inflammatory disease have captured our attention. A delayed diagnosis of an associated systemic rheumatologic disease might result in lethal complications. From previous reports worldwide, approximately 25% - 50% of non-infectious scleritis is related to systemic collagen vascular disease[2,3]; therefore, screening laboratory tests for rheumatoid factors, antinuclear antibodies, and ANCA have been recommended. In our study, 20% of our patients were diagnosed with scleritis as a presenting feature of systemic collagen vascular diseases. This is consistent with the finding of a report from the Ocular Autoimmune Systemic Inflammatory Infectious Study that scleritis occured in conjunction with a systemic collagen vascular disease might be lower in the Asian population.[6] Some of the 27.4% of our patients who lacked a laboratory investigation might have had an undiagnosed systemic rheumatologic disease, which would have affected the study results. RA has been reported to be by far the most common rheumatologic disease related to scleritis[2,4,6], although some other studies found that GPA was far and away the most prevalence.[5] We believe that ethnicity might play an important role in the differences in these results. Certain systemic diseases related to scleritis were found to have an association with the ocular prognosis; GPA had the worst visual outcomes, whereas RA and relapsing polychondritis had intermediate visual outcomes.[12] The two most common rheumatologic diseases found to be related to scleritis in this study were RA and non-specific ANCA associated disease. Our data demonstrated that diffuse anterior scleritis was the main type of scleral inflammation found with a systemic collagen vascular disease; this form of

TABLE 1. Demographics and characteristics of non-infectious scleritis patients.

Factors	Non-infectious scleritis (N=95 cases, 123 eyes)	Subgroup analysis Idiopathic group (N=51 cases, 70 eyes)	Systemic collagen vascular disease association group (N=18 cases, 27 eyes)	*P*-value
Age (years); (mean+/-SD)	46.60	45.06 (+/-12.1)	48.22 (+/-15.45)	0.379
Female	69 (72.6%)	40 (78.4%)	10 (55.6%)	0.074
Unilateral	67 (70.5%)	33 (47.1%)	9 (33.3%)	0.219
Recurrence	16 (16.8%)	19 (27.1%)	3 (11.1%)	0.085
BCVA (LogMAR) (median, range)				
First visit	0.1 (0-3)	0.1 (0-1)	0.1 (0-3)	0.041
Last visit	0.1 (0-2)	0.1 (0-2)	0.1 (0-2)	0.375
Scleritis type (eyes)				
Diffuse anterior	75 (60.98%)	40 (58.8%)	24 (88.9%)	0.005
Nodular anterior	34 (27.64%)	18 (26.5%)	3 (11.1%)	0.104
Posterior	11 (8.94%)	11 (16.2%)	0	0.026
Associated findings (eyes)				
PUK				
First visit	9 (7.32%)	9 (12.9%)	0 (0.0%)	0.058
Other visits	11 (8.94%)	10 (14.3%)	1 (3.7%)	0.281
Anterior uveitis				
First visit	38 (30.89%)	26 (37.1%)	10 (37%)	0.992
Other visits	14 (11.38)	11 (15.7%)	2 (7.4%)	0.343
Secondary OHT				
First visit	9 (7.32%)	5 (7.1%)	4 (14.8%)	0.259
Other visits	13 (10.57%)	7 (10%)	4 (21.1%)	0.180
Scleral thinning				
First visit	12 (9.76%)	8 (11.4%)	2 (7.4%)	0.722
Other visits	19 (15.48%)	8 (11.4%)	9 (33.3%)	0.017
Vitritis				
First visit	4 (3.25%)	3 (4.3%)	1 (3.7%)	0.815
Other visits	1 (0.81%)	1 (1.4%)	0 (0.0%)	1.0
CME				
First visit	3 (2.44%)	3 (4.3%)	0 (0.0%)	0.447
Other visits	2 (1.63%)	1 (1.4%)	0 (0.0%)	0.674
Exudative RD				
First visit	1 (0.81%)	1 (1.4%)	0 (0.0%)	0.674
Other visits	2 (1.63%)	2 (2.9%)	0 (0.0%)	0.550
Papillitis				
First visit	7 (5.69%)	7 (10%)	0 (0.0%)	0.186
Other visits	3 (2.44%)	3 (4.3%)	0 (0.0%)	0.992
Treatment				
Immunosuppressive therapy	25 (26.32%)	15 (29.4%)	10 (55.6%)	0.047

TABLE 2. Multivariate linear regression analysis between systemic collagen vascular disease association group and idiopathic group.

Parameters	Univariate analysis			Multivariate analysis		
	Odd ratio	CI	*P* value	Odd ratio	CI	*P* value
Female	0.31	0.096 to 0.97	0.044	NS	NS	NS
Age	1.02	0.98 to 1.06	0.36			
Bilateral	1.68	0.57 to 4.98	0.99			
VA (LogMAR)						
First visit	4.0	1.05 to 15.3	0.43			
		0.74 to 5.73				
Last visit	2.06	1.66				
Recurrence	0.37	0.08 to 1.73	0.21			
Associated findings						
PUK						
First visit	0.000001	0.000001 to 0.0000002	0.99			
		0.25 to 20.2				
Other visits	2.27		0.46			
AU						
First visit	0.93	0.31 to 2.8	0.90			
		0.29 to 7.77				
Other visits	1.49		0.64			
IOP > 21						
First visit	0.33	0.04 to 2.5	0.28			
		0.62 to 11.1				
Other visits	2.63		0.19			
Scleral thinning						
First visit	0.87	0.15 to 4.93	0.88			
		1.2 to 17.7				
Other visits	4.6		0.03	4.38	1.1 to 17.6	0.038
Vitritis						
First visit	1.44	0.12 to 16.9	0.77			
		NA				
Other visits	NA		NA			
CME						
First visit	0.0001	0.000001 to 0.000002	0.99			
		0.000001 to 0.00003				
Other visits	0.00001		1.0			
ERD						
First visit	0.0001	0.00001 to 0.00001	1.0			
		0.0001 to 0.002				
Other visits	0.001		0.99			
Papillitis						
First visit	0.001	0.0001 to 0.003	0.99			
		0.00001 to 0.0003				
Other visits	0.0001		0.99			
Scleritis type						
Diffuse	3.79	0.98 to 14.7	0.054	NS	NS	NS
		0.16 to 2.6				
Nodular	0.65	0.00002 to 0.0002	0.55			
Posterior	0.0001		0.99			

scleritis is universally the most common.[13] None of our patients were diagnosed with necrotizing scleritis, but as high as 15.48% of them developed subsequent scleral thinning without scleral melting or perforation. Most of them had a systemic rheumatologic disease association. Necrotizing scleritis was defined by Galor and Thorne as an area of scleral infarction and necrosis with or without typical signs of anterior scleritis (which depend on the type of necrotizing scleritis).[5] Given that definition, none of our patients had necrotizing scleritis even though they had scleral discoloration either in conjunction with, or without, signs of anterior scleritis at any time point. Galor and Thorne also explained that the bluish grey hue following anterior scleritis was not scleral thinning but instead a development of scleral collagen fiber rearrangement after inflammation.[5] The mechanism for the subsequent bluish discoloration of the sclera is unclear since there have been few studies on the scleral structure following an inflammation. A study by Kuroda et al., which described the optical coherence tomography of active anterior scleritis, reported that there was a swelling of the conjunctival stroma and episcleral layer without scleral thickening.[14] In contrast, Watson et al. reported that there was scleral edema with collagen fiber separation and infiltration of the inflammatory cells in the active stage of diffuse anterior scleritis.[15] Neither study reported any structural changes during the quiescence period. Further investigations to evaluate the pathophysiology of the subsequent scleral discoloration during the inactive stage of the scleral inflammation need to be considered in the future. Since there is a possibility of developing scleral thinning following a scleral inflammation and as the association is significantly higher among patients with concurrent systemic collagen vascular disease, we believe that aggressive treatment to halt disease progression is warranted. This is especially the case for patients who have a systemic collagen vascular disease, even if they do not initially present with necrotizing scleritis. A multidisciplinary approach is recommended to ensure the provision of a systematic assessment and sufficient treatments. We found that diffuse anterior scleritis had the highest association with systemic collagen vascular disease, which differs from some other reports that necrotizing scleritis had the highest association.[5,6] Based on our study findings, we urge clinicians to be aware of the high proportion of diffuse anterior scleritis found in patients who had a systemic collagen vascular disease, and of the chance of patients developing scleral thinning in cases of non-necrotizing anterior scleritis.

Limitations

As this was a retrospective study, incomplete data might have distorted its results. A sizeable proportion of our patients had not had a thorough investigation to rule out the possibility of there being an associated systemic inflammatory disease; thus, the percentage of patients who had scleritis in association with a systemic disease was probably underreported. Follow up duration of each patient was not reported and analyzed, which might also interfere with the study result. A further study with a larger number of patients would make the data analysis more reliable.

CONCLUSION

Scleritis can be a presenting sign of some systemic collagen vascular diseases. The pattern of scleral inflammation can be an indicator of the need to investigate for the presence of a more serious systemic disease. From this study, diffuse anterior scleritis was more likely to occur in conjunction with a systemic collagen vascular disease. Scleral thinning was found more frequently among patients who had a related systemic inflammatory disease; thus, an aggressive treatment should be considered in these patients.

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