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ORIGINAL ARTICLE

A Wide Spectrum of Ocular Manifestations Signify Patients with Systemic Sclerosis

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ABSTRACT

Objectives: Systemic sclerosis (SSc) is a rare, chronic connective tissue disease involving multiple organ systems, including the eye. We evaluated the detailed clinical ocular manifestations of outpatients with SSc.

Methods: Demographics, disease duration and subtype, nailfold capillaroscopy (NFC) patterns and laboratory parameters encompassing the autoantibody profile of 51 SSc patients were evaluated, and a general ocular examination was performed for each participant.

Results: Twenty-nine patients (56.86%) had eyelid skin alterations, 26 (50.98%) had retinal abnormalities, 26 (50.98%) had cataracts, 8 (15.69%) had conjunctival changes, 7 (13.73%) had iris abnormalities, 33 (64.71%) suffered from dry eye disease (DED), and 11 (21.57%) suffered from glaucoma. Significant positive correlations were found between NFC data and both tear breakup time and Ocular Surface Disease Index test values.

Conclusions: Eyelid skin abnormalities, DED and retinal abnormalities are among the most common SSc-related ocular involvements. Diverse ophthalmic findings are attributed to the heterogeneity of SSc.

Keywords: Dry eye disease, nailfold capillaroscopy, ocular findings, ocular manifestations, pathogenesis, scleroderma, systemic sclerosis

Systemic sclerosis or scleroderma (SSc) is a severe chronic connective tissue disease with diverse manifestations that is traditionally divided into 2 large subgroups: limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc).[1] Although the exact etiology remains unknown, three different pivotal sites are distinguished in its pathomechanism: generalized vasculopathy, characterized by obliteration of microvasculature and associated structural disease; an abnormal immunological response indicated by abnormal function of different T-lymphocytes, macrophages, and B-lymphocytes; and fibrosis due to the extreme synthesis of fibroblasts and deposition of extracellular matrix (ECM) proteins.[2] A consequence of these mechanisms is generalized tissue hypoxia and chronic ischemia.[3]

Due to the rarity of this disease, which does not particularly affect vision-related organs, only a few isolated case reports and overall studies have been reported, and these have involved small numbers of patients to describe the ophthalmological manifestations of SSc. There is great variability in the ophthalmic lesions observed in SSc: some are related to SSc (e.g.,

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eyelid skin abnormalities and dry eye disease [DED]), while others are considered controversial and most likely coincidental occurrences that are presumably not correlated with SSc (e.g., cornea guttata, or vitreous floaters).[4–6] The purpose of this study was to explore the clinically significant ocular manifestations of SSc in the outpatients of a tertiary referral center.

PATIENTS AND METHODS

This retrospective study was conducted by the Departments of Ophthalmology and Rheumatology at the University of Debrecen, Debrecen, Hungary. Consecutive patients with SSc diagnosed based on the corresponding international criteria[7] were recruited. Age at diagnosis and the disease duration of SSc patients were noted.

All patients involved in this study underwent a differential diagnostic assessment to exclude other systemic autoimmune diseases and did not fulfil the diagnosis of primary Sjögren syndrome according to the latest classification criteria.[8] A laboratory evaluation consisted of anti-Sjögren's syndrome-related antigen A (SSA) and anti-Sjögren's syndrome-related antigen B (SSB) antibodies, C-reactive protein (CRP), anticentromere antibody (ACA), antinuclear antibody (ANF), and anti-topoisomerase I (Scl-70) quantifications. For the classification of nailfold capillaroscopy (NFC) outcomes, 'early, active and late' patterns were identified.[9] Early was defined as the presence of few giant or enlarged capillaries, some capillary microhemorrhages and relatively well-preserved capillary distribution with no evident loss of capillaries. Findings were considered active if prevalent giant capillaries, frequent capillary hemorrhages, moderate loss of capillaries, and absent or mild ramified capillaries were reported. Finally, lesions were classified as late when severe loss of capillaries, extensive avascular areas, ramified or bushy capillaries, neoangiogenesis and disorganization of the normal capillary array occurred (Figure 1).

All patients were assessed by a comprehensive ophthalmological evaluation that included best corrected visual acuity (BCVA) measured using a Snellen chart. Broad beam examination of the slit lamp was performed to determine the condition of the ocular surface and surrounding tissues, and to observe changes in the eyelids, precorneal tear film, conjunctival impairments, cornea, anterior chamber, and iris. In addition, fundoscopy was conducted with photo documentation. To investigate the subjective symptoms of DED, the Ocular Surface Disease Index (OSDI) questionnaire (provided by Allergan Inc., Irvine, CA, USA)[10], which is accepted by the U.S. Food and Drug Administration (FDA) for use in clinical trials[11], was administered. This 12-item self-administered patient-reported outcome (PRO) scale

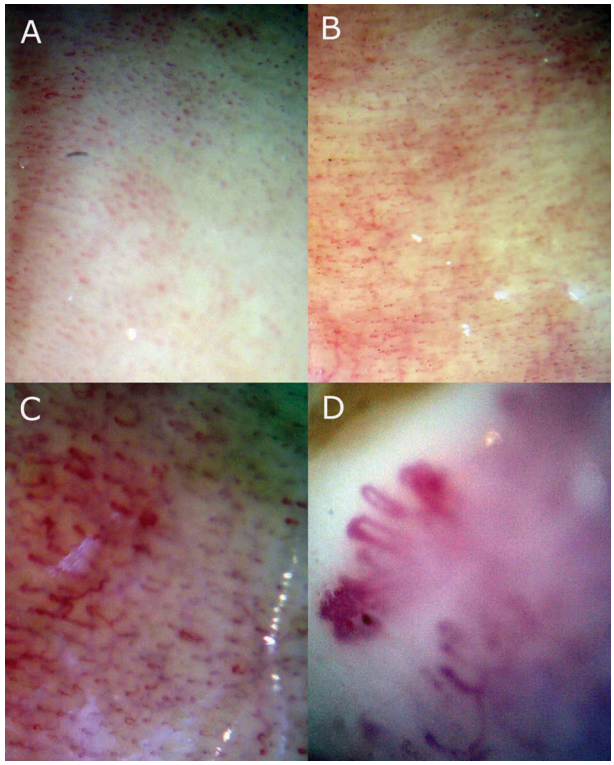

FIGURE 1. Normal-, early-, active-, and late-phase capillaroscopy patterns identified within the "scleroderma pattern". A: normal-; B: early-; C: active-; D: late-phase nailfold capillaroscopy patterns.

can be used to quantify the specific impact of DED on vision-targeted health-related quality of life (VT-HRQ). The questions examine three subscales of dry eye sensation: ocular discomfort, functioning, and environmental triggers. The overall OSDI score is calculated according to the questionnaire's algorithm and results in a total score ranging from 0 to 100, with 0–12 points considered normal, 13–22 points mild, 23–32 points moderate, and 33–100 points severe disease.

For tear film stability, tear film breakup time (tBUT) was measured. A strip of fluorescein (Haag-Streit, Koenitz, Switzerland) was moistened with a drop of unpreserved, sterile saline solution (0.9%) obtained from a single-dose ampule. This was then used to touch the inferior conjunctival fornix for a short time with minimal stimulation. The tear film was observed under cobalt blue-filtered wide light. The interval (seconds) between the last blink and the occurrence of the first dry spot was considered the tBUT value. Three measurements were obtained in each eye in each participant (both right and left eyes), and the average of these values was taken as the mean value. Values less than 10 seconds were considered abnormal.[12]

For the estimation of tear production, we used the unanesthetized Schirmer test, the Schirmer I test (ST_I), which was performed using standardized strips of filter paper (Alcon Laboratory, Fort Worth, TX, USA). Standard strips were inserted without any use of anesthetic at the lower-lid margin at the junction of

the middle and temporal third of both eyes while taking care not to touch the cornea. Patients were instructed to gently close their eyelids and to not move their eyes for 5 minutes; the strip was then removed, and the length of the wet portion was measured (mm/5 min). Three measurements were obtained in each eye in every participant (both right and left eyes), and the average of both side ST_I values was taken as the mean value. An ST_I value of less than 10 mm/5 minutes was considered abnormal.[13] Glaucoma was diagnosed and classified based on different diagnostic techniques. Peripapillary retinal nerve fiber layer (RNFL) thickness was determined by spectral domain optical coherence tomography (SD-OCT, Heidelberg Engineering, Heidelberg, Germany), and intraocular pressure (IOP) measurements were obtained using a noncontact tonometer (Huvitz HNT-1P, Huvitz, Dongan-gu, Republic of Korea). Regarding both RNFL and IOP quantifications, three measurements were obtained in each eye in each participant (both right and left eyes), and the average of these values was taken as the mean value. IOP was considered abnormal at >22 mmHg.

Automated static perimetry was performed using a Humphrey field analyzer (Carl Zeiss Meditec AG, Jena, Germany); both a 24–2 SITA standard test and a glaucoma hemifield program were carried out. A number of loss of fixation >2 was regarded as an exclusion criterion, and glaucomatous abnormality was defined as the presence of pattern deviation probability plots with <10%. Glaucoma was diagnosed if at least 1 of these 3 measurements was positive.

Conjunctival fornices were measured according to Jutley et al., and quantities that were 30% or more lower than those obtained in age-matched normal subjects were considered shallow.[14]

The study protocol was approved by the local ethics committee and performed in full compliance with the Good Clinical Practices (GCP) guidelines of the European Union, and the Declaration of Helsinki (1996). By signing a written informed consent form, all patients agreed to have study results regarding any side effects as well as possible risks and benefits of the study published.

Statistical Analyses

Continuous variables are expressed as the mean with standard deviation, whereas categorical variables are expressed as frequencies. The distribution of data was checked by using the Kolmogorov-Smirnov test. A nonparametric Mann-Whitney U test was used to compare continuous variables. The Chi^2 test and Fisher's exact test were used to compare categorical data. *P* values less than 0.05 were considered statistically significant. For the statistical analysis, IBM SPSS 24 statistical software (IBM Corp., Armonk, New York, USA) was used.

RESULTS

A total of 102 eyes of 51 (48 female and 3 male) consecutive patients diagnosed with SSc based on the corresponding international criteria (average age of 65.39 (SD±10.09) years old) were recruited into our study. All were recruited from the outpatient clinic of the Department of Rheumatology. Most patients had been suffering from SSc for a long time, with a mean disease duration of 18.45 ± 7.96 years. Forty-four patients were categorized as lcSSc and 7 as dcSSc, but since there was no significant difference between the manifestations of lcSSc and dcSSc patients, all the manifestations were treated as a whole, without partitioning into two major categories. All patients were of Caucasian origin. The characteristics and ocular data of the patients are presented in Tables 1 and 2.

Concerning systemic therapy, the patients were recently treated according to the latest therapeutic recommendations,[15] and they were therefore treated for only a short period and received low dose of methylprednisolone in order to prevent scleroderma renal crisis. However, as a consequence of the increased disease duration, most of the patients were formerly on steroid therapy.

Regarding ophthalmic diseases, only 2 patients (3.92%) had no ocular symptoms.

TABLE 1. Characteristics and clinical parameters of SSc patients. CRP: C-reactive protein; SSA: anti-Sjögren's--syndrome-related antigen A; SSB: anti-Sjögren's-syndrome-related antigen B; Scl-70: anti-topoisomerase I; ACA: anti-centromere antibody (only limited number of ACA evaluation was performed); ANA: antinuclear antibodies; ANF: antinuclear factor.

	Mean±SD
Age (years)	65.39 ± 10.09
Disease duration (years)	18.45 ± 7.96
CRP (mg/L)	4.91 ± 5.65
	No. (%)
Diffuse	7 (14)
Limited	44 (86)
SSA+	9 (17.6)
SSA-	42 (82.4)
SSB+	4 (7.8)
SSB-	44 (82.2)
Scl-70+	11 (21.6)
Scl-70-	40 (78.4)
ACA+	6 (11.76)
ACA-	45 (88.23)
ANA ANF+	35 (68.6)
ANA ANF-	16 (31.4)
Capillaroscopy	
abnormal	39 (76)
normal	12 (24)

TABLE 2. Visual acuity, IOP, tBUT, Schirmer and OSDI test values of the participants (mean±SD). BCVA: best corrected visual acuity; IOP: intraocular pressure; tBUT: tear film breakup time; s: second; OSDI: ocular surface disease index.

	Mean±SD
Visual acuity (BCVA)	0.75 ± 0.2
IOP (mmHg)	15.68 ± 2.12
tBUT (s)	6.6 ± 3.57
Schirmer I (mm/5 min)	7.07 ± 3.87
OSDI	21.56 ± 13.1

The leading ocular disorder was DED, which was found in 33 patients (64.71%); it was followed by eyelid skin changes, namely, stiffness, which was declared if the modified Rodnan skin score (mRSS)[16] was 3; tightness, which was assessed by the pinch test; telangiectasia, which was found in 56.86% of the patients, as well as crystalline lens opacification and retinal microvascular abnormalities (26 patients each; 50.98%). In the cataract group, eight patients (15.69%) had had bilateral cataract operation previously. Approximately one-fifth of the patients suffered from glaucoma (21.57%), and a wide spectrum of glaucoma types was detected: open-angle, closed-angle, pigmentary, and normal tension. Conjunctival changes, namely, shallow fornices, occurred in 15.69% of the patients. Two patients developed unilateral nodular episcleritis, and one developed anterior uveitis with ciliary flush. Regarding corneal alterations, one patient evolved keratoconus, a form of corneal ectasia that is often bilateral which was, in this case, asymmetrical. In this case, corneal cross-linking treatment had already been performed on the advanced side and was proposed on the other side. In addition, corneal scarring, dellen formation, and keratitis occurred. Diverse iris impairments, such as distorted blood vessels, atrophy, and transillumination, were also discovered. These data are shown in Table 3.

The results of the correlation analysis are shown in Table 4. In general, the association between laboratory parameters and ocular findings was weak. Interestingly, significant differences were found between NFC patterns and tBUT and OSDI parameters. The average tBUT value was 5.60 ± 2.67 in patients with abnormal NFC patterns and 7.56 ± 4.08 in patients with normal NFC patterns (p = .049). The results for OSDI scores were 27.28 ± 13.65 and 16.05 ± 10.01 (p = .004), respectively.

Moreover, there was also a significant difference between SS-A positivity and tear parameters, i.e., ST_I test values and OSDI scores. There were also substantial differences between objective signs and subjective symptoms of DED in cases that were SS-B positive and negative, but these differences were not found significant, most likely because there were only 4 SS-B-positive but 47 SS-B-negative patients.

DISCUSSION

SSc is a chronic, autoimmune, connective tissue disease that affects the skin and multiple organs, including the eyes and surrounding structures. A major achievement in recent years has been the validation of new ACR/EULAR classification criteria for SSc.[17] Primarily based on the extent of skin involvement,

TABLE 3. Ocular findings of SSc patients (number and %). PVD: posterior vitreous detachment; DED: dry eye disease; AMD: age-related macular degeneration; CACG: chronic angle-closure glaucoma; NTG: normal-tension glaucoma.

Ocular findings	No. (%)
Eyelid:	29 (56.86)
stiffness, tightness, telangiectasia, blepharitis, ciliary madarosis	
Conjunctiva:	8 (15.69)
blood vessel congestion, loss of fine vessels, episcleral and subconjunctival blood vessel dilation, shallow fornices	
Cornea:	6 (11.76)
dellen, keratitis, scar formation, keratoconus	
Iris:	7 (13.73)
iridocyclitis, distorted blood vessels, atrophy, transillumination	
Lens:	26 (50.98)
opacification, cataract	
Vitreous body:	7 (13.73)
floater, PVD, opacity	
Retina/choroid:	26 (50.98)
microvascular abnormalities, generalized vasculopathy, retinal pigment epithel atrophy, drusen, choroidal scar formation, AMD, epiretinal membrane, macular hole	
DED	33 (64.71)
Glaucoma:	11 (21.57)
POAG, pigmentary glaucoma, CACG, NTG	
Miscellaneous:	1–1 (0.98)
retrobulbar neuritis, oculomotor nerve palsy	

TABLE 4. Association between laboratory parameters, nailfold capillaroscopy pattern and ocular findings of SSc patients. BCVA: best corrected visual acuity; IOP: intraocular pressure; tBUT: tear film breakup time; OSDI: ocular surface disease index; SS-A: anti-Sjögren's-syndrome-related antigen A; SS-B: anti-Sjögren's-syndrome-related antigen B; Scl-70: anti-topoisomerase I; ACA: anti-centromere antibody; ANF: antinuclear factor.

	BCVA		IOP (mmHg)		tBUT (s)		Schirmer I (mm/5 min)		OSDI	
	Mean±SD	p	Mean±SD	p	Mean±SD	p	Mean±SD	p	Mean±SD	p
Age:										
>65 years (n = 32)	0.752 ± 0.204	0.814	15.56 ± 1.75	0.295	6.45 ± 3.16	0.696	6.86 ± 3.39	0.784	22.80 ± 13.57	0.344
≤65 years (n = 19)	0.747 ± 0.207		15.87 ± 2.67		6.844.25		7.42 ± 4.65		19.47 ± 12.34	
Disease duration:										
>15 years (n = 37)	0.775 ± 0.180	0.327	15.41 ± 2.13	0.058	6.26 ± 3.25	0.421	6.50 ± 3.50	0.199	20.95 ± 10.89	0.966
≤15 years (n = 14)	0.686 ± 0.250		16.39 ± 1.99		7.50 ± 4.31		8.57 ± 4.52		23.15 ± 18.11	
CRP:										
>3.2 mg/L (n = 19)	0.704 ± 0.217	0.150	15.74 ± 1.76	0.451	7.11 ± 4.07	0.616	7.55 ± 4.18	0.533	18.57 ± 10.28	0.331
≤3.2 mg/L (n = 32)	0.777 ± 0.196		15.50 ± 2.23		6.19 ± 3.27		6.74 ± 3.77		23.68 ± 14.47	
Diffuse (n = 7)	0.700 ± 0.191	0.460	17.64 ± 1.60	0.063	7.86 ± 5.67	0.546	8.07 ± 6.43	0.738	17.21 ± 19.20	0.098
Limited (n = 44)	0.758 ± 0.206		15.36 ± 2.04		6.40 ± 3.17		6.91 ± 3.39		22.25 ± 11.97	
SS-A+ (n = 9)	0.783 ± 0.132	0.725	15.33 ± 2.88	0.911	5.06 ± 3.88	0.076	**4.78 ± 3.42**	**0.036**	**32.41 ± 17.15**	**0.029**
SS-A- (n = 42)	0.744 ± 0.216		15.75 ± 1.96		6.93 ± 3.46		**7.56 ± 3.82**		**19.23 ± 10.98**	
SS-B+ (n = 4)	0.706 ± 0.244	0.608	17.25 ± 2.10	0.113	4.62 ± 1.97	0.225	5.75 ± 3.50	0.573	34.89 ± 19.20	0.099
SS-B- (n = 47)	0.754 ± 0.202		15.54 ± 2.09		6.77 ± 3.64		7.18 ± 3.92		20.42 ± 12.07	
Scl-70+ (n = 11)	0.754 ± 0.196	0.661	15.82 ± 1.86	0.290	6.27 ± 4.02	0.621	7.27 ± 4.80	0.954	17.49 ± 8.58	0.296
Scl-70- (n = 40)	0.749 ± 0.208		15.64 ± 2.21		6.69 ± 3.49		7.01 ± 3.65		22.68 ± 13.97	
ACA+ (n = 6)	0.858 ± 0.146	0.662	16.00 ± 2.05	0.664	7.17 ± 3.54	0.334	8.17 ± 4.75	0.131	23.04 ± 11.60	1.000
ACA- (n = 4)	0.862 ± 0.075		15.25 ± 0.17		5.12 ± 4.01		5.62 ± 5.95		29.68 ± 21.47	
ANF+ (n = 35)	0.739 ± 0.211	0.506	15.73 ± 2.34	0.713	6.53 ± 3.84	0.847	6.84 ± 4.21	0.348	21.51 ± 13.35	0.707
ANF- (n = 16)	0.777 ± 0.189		15.56 ± 1.59		6.75 ± 2.99		7.56 ± 3.06		21.67 ± 12.97	
Capillaroscopy pattern:										
abnormal (n = 39)	0.791 ± 0.208	0.051	15.44 ± 2.14	0.580	**5.60 ± 2.67**	**0.049**	6.36 ± 3.42	0.243	**27.28 ± 13.65**	**0.004**
normal (n = 12)	0.712 ± 0.195		15.90 ± 2.12		**7.56 ± 4.08**		7.75 ± 4.22		**16.05 ± 10.01**	

SSc is didactically classified into the following subtypes: limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc), which determine and define disease severity. In its limited form, distinctive skin changes are restricted to the elbows and knees or the face, while dcSSc is characterized by truncal and acral skin hardening (fibrosis) and associated with different issues in many organs of the body.[7] The incidences and estimates of prevalence vary geographically: higher and lower values have been recorded in populations with European and Asian ancestry, respectively. A female predominance was detected, as the female to male ratio ranges from 4.8:1 to 8:1.[18]

Ocular involvement has been reported in patients with SSc, mainly in case reports or some case series reports but only scant review articles.[4–6,19] Based on the diverse pathomechanisms observed in this condition, the disease can be characterized according to different ocular findings, some of which are vision-threatening. Ophthalmic manifestations are common, and may arise at any stage and can involve both the anterior and posterior segments of the eyeball and adnexa.[20]

To obtain more relevant information about ocular traits of SSc, a comprehensive survey was carried out among these patients.

Anterior Segment

Eyelid

The fact that eyelids and periorbital regions are frequently affected by SSc is well documented in the literature. In our study, the following types of eyelid alterations occurred: stiffness, tightness, telangiectasia and blepharitis (Figure 2A), which had an overall incidence rate of 56.86%, in good agreement with previous surveys.[5,6,19,21] Among the eyelid lesions most commonly reported in previous papers, namely, periorbital edema, ectropion and ciliary madarosis[22], only the latter was supported by our clinical data. Eyelid abnormalities are presumed to be related to SSc, and they could be more prevalent in the diffuse subtype of the disease.[19]

Conjunctiva/episclera

Containing more or fewer blood vessels the conjunctiva is also associated with SSc. Two main abnormalities occur: blood vessel congestion (Figure 2B) and the loss of fine vessels. In our survey, both occurred at the same rate as has been reported in previous studies.[5,19] However, episcleral and subconjunctival blood vessel dilation was observed in 3 patients (5.88%), indicating a lower rate compared to those

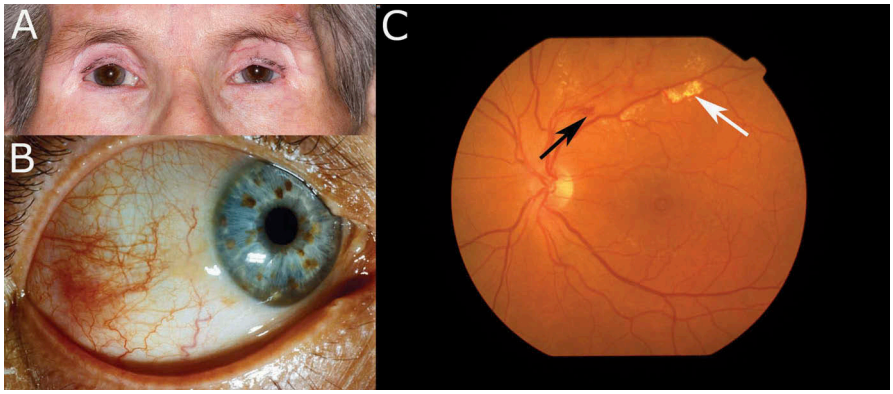

FIGURE 2. A. Eyelid stiffness, tightness, telangiectasia, madarosis, and blepharitis in the upper and lower eyelids of an SSc patient. B. Conjunctival and episcleral blood vessel congestion in a patient with SSc. C. Microvascular abnormalities (black arrow) and choroid atrophy (white arrow) on the fundus of an SSc patient. Additionally, a macular hole can be observed as an accessory finding, and was presumably not related to SSc.

reported in previous studies.[5,6] Shallow fornices, which are assumed to be connected to the underlying disease, were also present in a relevant ratio.

Cornea

Few publications have explored corneal involvement in SSc even though the cornea is inherently considerably exposed to the disease because of its large collagen content. Corneal lesions were first described in SSc by Coyle, who presented a case of corneal ulceration with encompassing keratitis.[23] Central corneal thickness (CCT) in conjunction with SSc has been surveyed in recent decades; nonetheless, outcomes are rather controversial. Serup and colleagues found that CCT was increased in SSc,[24] Gomes et al. did not observe any significant difference between the CCT of SSc patients and healthy controls,[25] and Şahin and coworkers found that CCTs were thinner in SSC patients.[26] We also evaluated all pachymetric and corneal volume parameters and found that several other anterior segment quantities were decreased.[27] Corneal ectatic disorders, such as keratoconus, have also been associated with SSc; although they are defined as noninflammatory progressive diseases of the cornea, strong associations between keratoconus and various immune-related disorders have been described.[28] Keratoconus was first found to occur in SSc patients in a recent case report by Anayol et al.[29] Because the incidence of keratoconus is relatively low in the normal population, in which it occurs in an estimated 13.3 cases per 100,000,[30] the importance of corneal alterations in SSc seems to be further emphasized by our study, in which one patient manifested keratoconus, and other cases showed with corneal scar formation, e.g., dellen, and severe keratitis. Other infrequent corneal lesions, such as filamentous keratitis,[5] bilateral peripheral ulcerative keratitis,[31] pellucid marginal degeneration[32] or keratomalacia[33], have also been described.

Iris

Because SSc is characterized by massive systemic and progressive vasculopathy and the iris is a part of the uveal tract, this tissue is a site predisposed to SSc manifestations. In our survey, 7 patients (13.73%) had iris abnormalities, with most of them irregular, and associated with distorted blood vessels, atrophy or transillumination, with an incidence rate comparable to those published in former studies.[5,19] Iris transillumination can exist in every zone and it is considered to be an abnormality of the iris epithelium.[5,6,21]

Cataract

Concerning visual acuity, the majority of our study population had satisfactory vision; however, cataracts occurred in 50.98% of the patients' eyes, and this is a higher rate than is indicated by international standards. For example, in the Framingham Eye Study, a survey carried out in the largest population of persons of European descent to investigate crystalline lens opacification, cataract formation occurred in an average of 8.4% of the population.[34] In our study, pseudophakic intraocular lenses had already been implanted in 15.38% of the patients' eyes, and a further 35.6% suffered from cataracts. Cataract development in SSc patients could, nevertheless, be partially attributed to systemic corticosteroid administration since even though the latest therapeutic recommendations restrict corticosteroid application because of scleroderma renal crisis (SRC), in return the average disease duration is nearly twenty years, and as a consequence, patients who suffer from SSc over a longer period will definitely have been administered steroids. In conclusion, cataracts are basically expected to occur due to age and are not thought to be related to the underlying disease, but are instead secondary to corticosteroid treatment.[18]

Posterior Segment

Vitreous Body

Because it is an avascular tissue consisting of approximately 98% of water[35], all the vitreous body alterations we observed (namely floaters, or posterior vitreous detachment (PVD)) are proposed to be related to age rather than SSc.

Retina/choroid

Generalized vasculopathy plays an important role in the pathomechanism of SSc, and this fact is particularly supported by the large portion of cases with microvascular abnormalities in the retina and choroid (Figure 2C). In our study, different forms were found, ranging from mild retinal pigment epithelial atrophy to drusen or choroidal scar formation and severe age-related macular degeneration (AMD). The retinal blood vessel irregularities observed in SSc are highlighted by the finding of a possible relationship between SSc and ocular diseases that was first mentioned in 1953 in a case report by Agatston, who observed retinal cystoid bodies.[36] However, it must be emphasized that the retinal and choroidal findings observed in SSc are declared equivocal in that their relatedness to the underlying disease cannot be excluded; nevertheless, some of them are expected to be related to age and systemic hypertension. Consequently, further clinical studies and histopathological evaluations are needed to verify or reject any such possible relationship.

Glaucoma

Allanore et al. conducted a study to investigate the prevalence of ocular glaucomatous abnormalities in SSc and found that glaucomatous neuropathy without ocular hypertension was dramatically more common in SSc patients than in controls.[37] Yamamoto and colleagues examined the prevalence of normal-tension glaucoma (NTG) and primary open-angle glaucoma (POAG) in patients with collagen diseases and concluded that 8 out of 153 patients (5.23%) were of concern, while 2 patients with SSc had been on systemic corticosteroid therapy.[38] In a recent survey, Gomes et al. described 23% patients with glaucoma in SSc and suggested that systemic vascular disturbances were a potential reason for its occurence.[39] In our study, glaucoma was found in 11 (21.57%) patients. While our results are thus comparable to the literature, it is worth noting that different types of glaucoma were present from POAG to pigmentary glaucoma and NTG.

DED

In addition to eyelid skin abnormalities, DED is considered to be the most common ocular manifestation of SSc. Fibrosis-related impairment of the main lacrimal gland secretion can cause a quantitative lack of the precorneal tear production. Moreover, chronic blepharitis and Meibomian gland dysfunction (MGD) can result in further tear film anomalies. Gomes and coworkers reported that DED has a moderate impact on vision-related quality of life in patients with SSc.[40] However, in a study by Stucchi and Geiser, DED was not found among SSc patients,[41] and numerous surveys have demonstrated that DED is a leading ocular manifestation of SSc. In Horan's study, 47.82% of the patients had decreased tear secretion; however, only 30.43% of them suffered from DED.[5] In analyzing the ocular manifestations of 26 SSc patients, Rasker et al. observed signs of DED in 9 patients (34.62%).[42] Wangkaew et al. investigated signs of DED in Thai patients with different rheumatic and autoimmune diseases and found that they were present in 54% of SSc patients.[43] In general, DED has been confirmed to have a significantly higher prevalence among SSc patients. A total of 14.6% of people were found to have symptomatic DED in The Salisbury Eye Evaluation Study, a report that investigated the largest normal population to date to evaluate the presence of DED.[44] In examining objective signs and subjective symptoms of DED in SSc patients, the authors of another study found a positive correlation between subjective symptoms and disease duration.[45] In our study, a significant association was detected between NFC data and both tear film stability and subjective symptoms of DED. Because some NFC attributes are relevant to DED, these findings require further investigation to determine whether NFC is an applicable supplementary diagnostic tool for DED.[46]

Miscellaneous

Occasionally, some rare diseases, such as retrobulbar neuritis, or oculomotor nerve palsy, also occurred in our study population, but their incidences were similar to those reported in the normal population. All of them were therefore presumed to be unrelated to SSc.

CONCLUSIONS

Immunologically, the eye is viewed as a unique organ due to its complex structure. Consequently, altered immunological processes play an equally important role in the formation of ocular manifestations and other processes. Generalized vasculopathy is expected to cause alterations in the posterior

segment and uveal tract, while fibrosis-related impairments are thought to influence manifestations of the anterior segment and adjacent area. Ocular manifestations can be distinguished as primary, secondary, and coincidental. Primary manifestations, e.g., DED, shallow conjunctival fornices, or retinal microvascular abnormalities, are temporarily related to activities associated with SSc. Secondary manifestations are due to primary manifestations, and include posterior subcapsular cataract formation as a result of corticosteroid administration, or scleromalacia due to episcleritis, or underlying vasculitis, while coincidental manifestations are ocular disorders that are not connected to SSc. According to currently available data, this group contains pterygium, vitreous body abnormalities, or epiretinal membranes, etc.

In summary, the diverse ocular findings show that SSc exists along a wide spectrum ranging from its most common manifestations, such as skin abnormalities, DED, or retinal microvascular abnormalities, to rare iris abnormalities that are attributed to the heterogeneity of SSc. Moreover, a significant association was confirmed between NFC data and both tear film stability and the subjective symptoms of DED.

In our study, less than 4% of the SSc patients had no ocular symptoms. Because it is sometimes difficult to determine whether a clinical sign is related to the underlying disease, further investigations are needed to ascertain or reject a potential relationship. The leading ocular disorder was DED, which was followed by eyelid skin changes and cataract formation; however, the latter is basically expected to occur with age and it is not assumed to be connected to the underlying disease. The retinal and choroidal findings observed in SSc have mainly been declared to be indeterminate, and some of them are expected to be associated with age and systemic hypertension rather than SSc. Our results regarding glaucoma are comparable to those reported in the literature; nevertheless, it is remarkable that diverse glaucoma forms were present.

The eye is a sensitive marker for the onset or exacerbation of an immune reaction in many rheumatic and connective tissue diseases. Hence, clinicians must be aware of the diverse spectrum of the eye and adnexa involvement in SSc, and accordingly include ocular investigations into their routine practice. Early recognition and appropriate treatment can prevent sight-threatening complications or other significant abnormalities in addition to help maintain patients' quality of life.

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DECLARATION OF INTEREST

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

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