CLINICAL SCIENCE

Ocular findings in patients with systemic sclerosis

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OBJECTIVE: To evaluate the frequency and characteristics of ocular manifestations in outpatients with systemic sclerosis.

METHODS: In this cross-sectional study, 45 patients with systemic sclerosis were enrolled. Data regarding demographics, disease duration and subtype, age at diagnosis, nailfold capillaroscopic pattern and autoantibody profile were collected, and a full ophthalmic examination was conducted. Parametric (Student's t-test) and nonparametric (Mann-Whitney U test) tests were used to compare continuous variables. Fisher's exact test was used to compare categorical data. P values < 0.05 were considered significant.

RESULTS: Twenty-three subjects (51.1%) had eyelid skin changes; 22 (48.9%) had keratoconjunctivitis sicca, 19 (42.2%) had cataracts, 13 (28.9%) had retinal microvascular abnormalities and 6 (13.3%) had glaucoma. Eyelid skin changes were more frequent in patients with the diffuse subtype of systemic sclerosis and were associated with a younger age and an earlier age at diagnosis. Cataracts were presumed to be age-related and secondary to corticosteroid treatment. There was no association between demographic, clinical or serological data and keratoconjunctivitis sicca. The retinal microvascular abnormalities were indistinguishable from those related to systemic hypertension and were associated with an older age and a severe capillaroscopic pattern.

CONCLUSIONS: Eyelid skin abnormalities and keratoconjunctivitis sicca were the most common ocular findings related to systemic sclerosis. Some demographic and clinical data were associated with some ophthalmic features and not with others, showing that the ocular manifestations of systemic sclerosis are characterized by heterogeneity and reflect the differences in the implicated pathophysiological mechanisms.

KEYWORDS: Systemic scleroderma; systemic sclerosis; ocular findings; ocular manifestations; ophthalmologic findings.

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INTRODUCTION

Systemic sclerosis (SSc) is a generalized connective tissue disease of unknown origin with heterogeneous manifestations. It affects different organs and therefore requires interdisciplinary diagnostic and therapeutic management.[1]

In the pathophysiology of SSc, three abnormalities have been distinguished: 1) a fibroblast dysfunction leading to increased deposition of extracellular matrix; 2) a vascular abnormality resulting in tissue hypoxia; and 3) an immune response, manifested as altered T- and B-lymphocyte function and autoantibody production.[2-5]

Because SSc is a rare disease, most of the data regarding ocular involvement consist of single case reports or small case studies, thereby limiting the generalization of the findings to a larger population of patients.[6,7]

Recently, a narrative review conducted by Tailor et al. reported a wide variability of ophthalmic features in SSc. Some of these are well-known (i.e., eyelid skin changes and keratoconjunctivitis sicca), while others are controversial (primary SSc retinopathy).[8]

The purpose of this study was to evaluate the frequency and characteristics of ocular manifestations in outpatients with SSc.

PATIENTS AND METHODS

This cross-sectional study included all consecutive outpatients with SSc attending the rheumatology service at Clementino Fraga Filho University Hospital in Rio de Janeiro, Brazil, between April 2009 and December 2009. All patients fulfilled the American College of Rheumatology criteria for SSc (Box 1).[9]

Patients with SSc sine scleroderma, scleroderma overlap syndrome, diabetes mellitus or severe systemic hypertension were excluded.

Box 1 - American college of rheumatology diagnostic criteria for systemic sclerosis.[9]

Major criterion

- Proximal sclerodermatous skin changes (proximal to the metacarpophalangeal joints)

Minor criteria

- Sclerodactyly
- Digital pitting scars of fingertips or loss of substance of the distal finger pads
- Bibasilar pulmonary fibrosis

* The patient should fulfill the major criterion or two of the three minor criteria.

Data regarding age, gender, SSc subtype (as defined by LeRoy et al.),[10] disease duration, age at diagnosis, nailfold capillaroscopic pattern,[11] autoantibody profile (antinuclear, anti-topoisomerase I, anti-centromere antibodies), systemic corticosteroid or chloroquine use, systolic and diastolic blood pressure, ocular symptoms and detailed ophthalmic history were recorded. All patients underwent a complete ophthalmic evaluation by the same physician, who was unaware of the patients' clinical and laboratory data.

The capillaroscopic findings were classified as either mild or severe. Mild findings were characterized by the presence of giant capillaries, capillary microhemorrhages and a relatively well-preserved capillary distribution. There was moderate or no capillary loss, ramified capillaries were absent or mildly branched and the capillary architecture was mildly disorganized. Severe findings were characterized by the near-absence of giant capillaries and microhemorrhages, and they involved a severe loss of capillaries and the development of extensive avascular areas, ramified and bushy capillaries (indicative of neoangiogenesis) and severe disorganization of the normal capillary array.

The best-corrected visual acuity (BCVA) for distance was assessed using the Snellen chart, and the BCVA for near vision was assessed with Jaeger charts. After the vision assessment, cover test and ocular motility examination, biomicroscopy was performed.

Dry eye evaluation was performed in the following sequence: tear break-up time (TBUT), Schirmer I test and Rose Bengal (RB) staining.

TBUT was measured after 1% fluorescein (Fluoresceína™, Allergan, São Paulo, SP) instillation. The mean value of a total of 3 measurements was recorded.

A five-minute conventional Schirmer I test without anesthesia was performed on closed eyes by placing a commercially available 5 × 35-mm paper strip (Schirmer strips ™, Ophthalmos, São Paulo, SP) over the lower lid margin at the junction of the middle and lateral third of the lower lid margin and into the tear film.

RB staining was performed by touching the inferotemporal bulbar conjunctiva with a RB strip (Rose Glo ™, Rose Stone Enterprises, Alta Loma, CA) dampened with one drop of a preservative-free isotonic sodium chloride solution. The reaction was classified according to the van Bijsterveld scoring system.[12]

Abnormal test values were as follows: Schirmer test $\leq$ 5 mm in 5 minutes, TBUT $<$ 10 seconds and RB score $>$ 3. Patients were diagnosed with definite keratoconjunctivitis sicca (KCS) if two or more tests were abnormal and with probable KCS if only one test was abnormal. The diagnosis of KCS in this study was made by extrapolating the Japanese[13] and Copenhagen criteria.[14]

Intraocular pressure (IOP) was measured by Goldmann applanation tonometry. Indirect ophthalmoscopy was performed with an indirect ophthalmoscope and a 20-diopter lens after both pupils were dilated with 1% tropicamide. The posterior pole was further evaluated by slit-lamp biomicroscopy using a 78-D Volk lens.

All patients with suspected glaucoma (IOP $>$ 21 mmHg in either eye or IOP difference $>$ 5 mmHg between the two eyes or optic disc suspicious for glaucoma) underwent a gonioscopy and automated perimetry using a Humphrey field analyzer. The glaucoma definition that was adopted has been defined elsewhere.[15,16]

Statistical analyses were performed using JMP statistical software (Version 8.0, SAS Institute Inc., USA). Continuous variables were expressed as the mean $\pm$ standard deviation, whereas categorical variables were expressed as frequencies and their percentages. Parametric (Student's t-test) and nonparametric (Mann-Whitney U) tests were used to compare continuous variables, according to the data distribution. Fisher's exact test was used to compare categorical data. P values $<$ 0.05 were considered significant.

RESULTS

Forty-five patients were enrolled in this study. The study population was between 22 and 77 years old, with an average age of 51 years. Table 1 shows the demographics of the study population.

Regarding ophthalmic history, two patients had a history of recurrent mild episcleritis, and one patient had a history of central retinal vein occlusion.

Of the 45 patients, 12 (26.7%) had no ocular symptoms. Among the patients with ocular symptoms, 11 (24.4%) complained of decreased vision, 6 (13.3%) of itching, 6 (13.3%) of burning, 6 (13.3%) of ocular pain, 5 (11.1%) of foreign body sensation, 4 (8.9%) of dry eye, 4 (8.9%) of increased tearing, 3 (6.7%) of floaters, 2 (4.4%) of redness and 1 (2.2%) of photophobia.

The majority (85.0%) of patients had BCVAs of 20/30 or better. Four (8.9%) patients had BCVAs of 20/80 or worse in at least one eye. Low visual acuity was bilateral and caused by cataracts in three of these patients. One patient had low visual acuity due to irregular corneal astigmatism developed after a radial and transverse keratotomy procedure.

Table 1 - Demographic features of the study population.

Characteristics	Study population
Average age (yr)	51.0
Range	22-77
SD	12.6
Gender, n (%)	
Female	40 (88.9)
Male	5 (11.1)
SSc subtype, n (%)	
Limited	27 (60.0)
Diffuse	18 (40.0)
Average duration of SSc (yr)	10.9
SD	9.2

Table 2 - Prevalence of ocular findings.

Ocular finding	No.	%	Presumed to be related to SSc
Eyelid stiffness or tightness	23	51.1	yes
Eyelid telangiectasia	23	51.1	yes
Blepharitis	18	40.0	no
Blepharophimosis	1	2.2	yes
Pinguecula	37	82.2	no
Pterygium	7	15.6	no
Shallow fornices	7	15.6	yes
Conjunctival vascular congestion	4	8.9	yes
Loss of fine conjunctival vessels	2	4.4	yes
Keratoconjunctivitis sicca	22	48.9	yes
Cornea guttata	2	4.4	no
Corneal irregular astigmatism	1	2.2	no
Open-angle glaucoma	5	11.1	yes
Angle-closure glaucoma	1	2.2	no
Iris transillumination defects	4	8.9	yes
Cataract	19	42.2	no
Pseudophakia	2	4.4	no
Retinal microvascular abnormalities	13	28.9	yes*
Drusen	2	4.4	no
Central retinal vein occlusion	1	2.2	yes*
Chorioretinal scar	1	2.2	no
Congenital hypertrophy of the RPE	1	2.2	no
Orbital fat atrophy and enophthalmos	3	6.7	yes
Orbital varices with conjunctival varices	1	2.2	no

RPE = retinal pigment epithelium
*Also related to age and systemic hypertension

Regarding biomicroscopy and fundoscopy evaluation, several ocular findings were found and are summarized in Table 2. In considering the large variety of ocular findings revealed in this study, some distinctions were made between those that were probably related to SSc and those that presumably were not (Table 2).[8]

Eyelid stiffness was associated with difficulty in lid eversion and a woody texture upon palpation. Comparing patients with and without eyelid stiffness (Table 3), we found that the mean age and the age at diagnosis were significantly lower in the former group ($p = 0.01$ and $p = 0.03$, respectively). The diffuse subtype was more prevalent among patients with eyelid skin changes ($p = 0.03$).

Cataracts were found in 19 (42.2%) patients. The majority were classified as a nuclear lens opacity, and the mean age of patients with cataracts was 59.2 $\pm$10 years, 14.9 years older than patients without cataracts ($p < 0.001$). Additionally, 89.5% of the patients with cataracts were either currently taking or had previously taken systemic corticosteroids, compared with 60.0% of the patients who did not have cataracts ($p = 0.04$).

The prevalence of glaucoma was 13.3%; 5 (11.1%) patients had open-angle glaucoma, and 1 (2.2%) had angle-closure glaucoma. The mean IOP was 14.0 $\pm$ 3.4 mmHg and ranged from 8 to 24 mmHg. Among patients with glaucoma, 4 (66.7%) were either currently taking or had previously taken systemic corticosteroids, compared with 75.7% of those without glaucoma ($p = 0.64$).

Cornea guttata was found in 2 patients, aged 72 and 77 years old. Spotty areas of iris transillumination, present in all zones of the iris, were reported in 4 patients and were not associated with diabetes, intraocular surgery, moderate/severe myopia or other causative factors for iris changes.

Regarding dry eye evaluation, as many as 38 (84.4%) patients had TBUT < 10 seconds and 19 (42.2%) patients had

Table 3 - Comparison of demographic, clinical and laboratory data between patients with and without eyelid stiffness; with and without keratoconjunctivitis sicca; and with and without retinal microvascular findings.

	Eyelid stiffness			KCS			Retinal vascular findings		
	Present (n = 23)	Absent (n = 22)	P	Present (n = 22)	Absent (n = 23)	p	Present (n = 13)	Absent (n = 32)	p
Gender (female/male)	19/4	21/1	0.35 †	19/3	21/2	0.67 †	12/1	28/4	0.99 †
Mean age (years)	46.3	56.0	0.01§	53.5	48.7	0.21§	59.5	47.6	0.003§
Mean disease duration (years)	10.4	11.4	0.96¶	13.7	8.2	0.15¶	14.8	9.3	0.11¶
Mean age at diagnosis (years)	35.9	44.6	0.03§	39.8	40.5	0.87§	44.7	38.3	0.15 §
Disease type									
Limited/diffuse(n) (%)	10/13 (43.5/56.5)	17/5 (77.3/22.7)	0.03†	13/9 (59.1/40.9)	14/9 (60.9/39.1)	0.99†	7/6 (53.8/46.2)	20/12 (62.5/37.5)	0.74 †
Antibodies profile positive/tested (%)									
Antinuclear antibodies	19/21 (90.5)	12/17 (70.6)	0.21†	16/19 (84.2)	15/19 (78.9)	0.99†	8/10 (80.0)	23/28 (82.1)	0.99 †
Anticentromere antibodies	3/22 (13.6)	4/18 (22.2)	0.68†	4/20 (20.0)	3/20 (15.0)	0.99†	3/12 (25.0)	4/28 (14.3)	0.41†
Antitopoisomerase I antibodies	8/21 (38.1)	3/19 (15.8)	0.16†	6/19 (31.6)	5/21 (23.8)	0.73†	3/12 (25.0)	8/28 (28.6)	0.99 †
Capillaroscopic pattern/tested (%)									
Mild	8/15 (53.3)	8/13 (61.5)	0.72†	7/15 (46.7)	9/13 (69.2)	0.28†	1/8 (12.5)	15/20 (75.0)	0.004†
Severe	7/15 (46.7)	5/13 (38.5)		8/15 (53.3)	4/13 (30.8)		7/8 (87.5)	5/20 (25.0)	

† = Fisher's test; § = T-test; ¶ = Mann-Whitney U-test
KCS = Keratoconjunctivitis sicca

Schirmer I test values $\leq$ 5 mm after 5 minutes in at least one eye. Total RB staining ranged between 0 and 5. RB scores >3 were found in 4 (8.9%) patients, while scores ≥ 1 were found in 22 (48.9%) patients. According to the criteria adopted in this study, 22 patients (48.9%) had a definite and 17 (37.8%) had a probable diagnosis of KCS. There were no significant differences in the studied variables between those with a definite KCS diagnosis and those without, as seen in Table 3.

Retinal microvascular abnormalities were found in 13 (28.9%) patients and included generalized and focal arteriolar narrowing, arteriovenous nicking, and vascular tortuosity. A 72-year-old patient had an old central retinal vein occlusion, characterized by the presence of anastomotic vessels at the disc and a few residual hemorrhages.

In this study, 26 (57.8%) patients had a diagnosis of systemic hypertension. The mean systolic blood pressure in patients with retinal microvascular abnormalities was 124.3 ± 17.6 mmHg; in patients without retinal microvascular abnormalities, it was 119.9 ± 13.5 mmHg ($p = 0.22$). The diastolic blood pressure in patients with retinal microvascular changes also did not differ significantly from the diastolic blood pressure of patients without them (78.5 ± 9.0 mmHg versus 75.2 ± 8.7 mmHg, $p = 0.14$). Significantly more patients with retinal microvascular abnormalities were diagnosed with systemic hypertension than those without retinal microvascular abnormalities (100% versus 40.6%, $p < 0.001$). None of the patients had renal failure. The mean age of patients with retinal microvascular changes was 11.9 years older than that of patients without these changes ($p = 0.003$). In addition, patients with retinal microvascular findings had a higher prevalence of a nailfold capillaroscopic pattern, classified as a severe pattern (87.5% versus 25.0%, $p = 0.004$), as shown in Table 3. After adjusting for age and a systemic hypertension diagnosis, the presence of retinal signs was still significantly associated with a severe capillaroscopic pattern ($p = 0.02$).

None of the 11 (24.4%) patients who had been treated with chloroquine at some point in the disease course had chloroquine-related maculopathy.

DISCUSSION

Ocular findings in patients with SSc have been reported in several case reports and in a small number of case series. In an attempt to obtain more relevant information about the ocular features of SSc, we evaluated 90 eyes of 45 patients with SSc. To the authors' knowledge, the associations of demographic, clinical and serological data with eyelid abnormalities and KCS in SSc have not been previously reported, and the associations with retinal findings have only been reported in one previous study.

Our findings regarding eyelid skin changes (seen in 51.1% of the patients) correlate well with previous studies that showed a prevalence ranging from 29 to 65% of patients.[6-8] The most strikingly apparent ocular manifestation of SSc is the fibrotic change seen in the eyelids.[8,17] Skin fibrosis is the hallmark of SSc and is defined as excess deposition and accumulation of extracellular matrix, mainly type I collagen, in the dermis.[3] Tailor et al. have shown that skin fibrosis in SSc patients can result in a spectrum of clinical alterations ranging from lid stiffness or tightness to blepharophimosis or lagophthalmos.[8]

As expected, we found that eyelid skin changes occurred most commonly in patients who had more extensive skin involvement; that is, those with the diffuse subtype of SSc.[18] Interestingly, we also found that the patients with lid stiffness were significantly younger and had an earlier disease onset. It is well known that the diffuse subtype is associated with a worse prognosis and an earlier disease onset.[10,18,19] However, our study found no significant association between the subsets of SSc and the presence of either KCS or retinal microvascular abnormalities.

In previous studies, the extent of skin sclerosis was revealed to be a useful marker of severity and prognosis.[3] At present, the modified Rodnan skin score (mRSS) is considered the most appropriate and reproducible technique for measuring skin involvement using palpation in SSc.[18] Because the face is affected in both limited and diffuse SSc, future studies should address the mRSS in SSc patients to evaluate whether eyelid stiffness is related to either a higher total mRSS score or a higher facial skin score.

Over the last decade, studies have identified an association between autoantibodies and specific phenotypes of SSc and, thus, prognosis.[20] We found a lack of correlation between the autoantibody profile and the presence of eyelid stiffness, KCS, or retinal microvascular changes. We believe further studies should be conducted to elucidate these associations. Previous studies have shown correlations between sicca syndrome and anti-Ro/SSa antibodies in patients with SSc.[21] Anti-Ro/SSA antibodies were not investigated in this study. The relation between anti-Ro/SSA antibodies and KCS in SSc patients should be investigated further.

In this study, symptoms usually related to dry eye, such as itching, burning, foreign body sensation, dryness, and redness, were reported by 29 (64.4%) patients and were the most common complaint. Alarcon-Segovia et al.[22] studied the prevalence of Sjogren's syndrome in patients with SSc. They found that of 25 patients with SSc, 18 (72%) described dry eye symptoms.[22]

Depending on the study, the prevalence of SSc patients with KCS varies considerably (37 to 79%),[6,7,8,22,23] and the prevalence found in this study (48.9%) was well within this range. The observed variation may be partly due to the KCS definition used and partly due to demographic differences in the patient populations. A previous study showed that patients with SSc have a higher prevalence of KCS than controls (47.8 versus 4.3%, $p<0.01$).[7]

To the best of our knowledge, the frequencies of blepharitis, pterygium and pinguecula in a population of SSc patients have never been reported before. The prevalence of blepharitis found in this study does not appear to differ markedly from that found in the general population.[24] Reports show geographical variation in rates of pterygium (from 1.2 to approximately 33%).[25-27] The prevalence of pinguecula has been reported to be as high as 70% in some areas.[25] Sun exposure plays an important role in the development of these two conditions, and reports indicate higher prevalence rates in tropical areas of the world, such as Brazil.[26,27] Therefore, the high prevalence of these conditions found in this study is in agreement with expectations for the general population of this area and is presumably not related to SSc.

West and Barnett studied ocular involvement in 38 patients with scleroderma[6] and found that conjunctival abnormalities, such as injection and vascular sludging, could be related to SSc, as these abnormalities seem similar to changes described in the SSc pattern for nailfold

capillaries.[6] In our study, we found conjunctival vascular congestion (8.9%) and a loss of fine conjunctival vessels (4.4%). In addition to conjunctival vascular abnormalities, patients with SSc may also present subepithelial fibrosis, leading to shallowing of the fornices.[7,8,17] This was observed in 15.6% of the patients in our study.

Inflammatory conditions, such as uveitis, episcleritis, scleritis and peripheral ulcerative keratitis, are well-recognized manifestations of connective tissue disease and have been reported in SSc patients.[7,8,28,29,30,31,32] In this study, 4.4% of the patients had a history of recurrent episcleritis. We did not find any signs of SSc-related uveitis in our sample. Instead, we found a chorioretinal scar due to ocular toxoplasmosis. Indeed, the association between SSc and uveitis is rare, and only single case reports have been reported in the peer-reviewed literature.[29-31]

In a population study, 0.6% of Maryland residents were found to have scars consistent with ocular toxoplasmosis. In Brazil, 1.2 to 17.7% of the population has been found to have retinal lesions suggestive of ocular toxoplasmosis. Thus, it is very unlikely that chorioretinal scars are related to SSc.[33]

Although previous reports suggest that some corneal abnormalities could be related to SSc, such as exposure keratitis (secondary to lid changes),[7] peripheral ulcerative keratitis,[8,32] pellucid marginal degeneration,[34] and biomechanical abnormalities,[35] our findings of cornea guttata (4.4%) and irregular astigmatism (2.2%) were not considered to be related to SSc.

Cornea guttata was found in two aged SSc patients. The frequency of cornea guttata increases with age and has been reported to be as high as 11% for women older than 50 years. The irregular astigmatism found in one patient was a complication of a radial and transverse keratotomy procedure.[36]

The prevalence of open-angle glaucoma was 11.1%, higher than reported for the general Brazilian population (2.4%).[37] Other studies have suggested that collagen disease, including SSc, may be a risk factor for developing both primary open-angle glaucoma and normal-tension glaucoma.[38,39] Because we performed only a single IOP measurement, we were unable to differentiate cases of normal-tension glaucoma from high-pressure, open-angle glaucoma.

Several manifestations of SSc, including Raynaud's phenomenon, digital ulceration, scleroderma renal crisis and pulmonary arterial hypertension, are caused by vascular abnormalities.[2] Although the pathogenesis of glaucomatous optic neuropathy is still controversial, there is increasing evidence that ischemia and vascular deregulation are implicated in the mechanisms underlying glaucoma.[40] Both SSc itself and systemic therapy with corticosteroids may lead to a higher prevalence of glaucoma. However, in this study, corticosteroid therapy was not associated with the diagnosis of glaucoma.

A study by Allanore et al. demonstrated an increased rate of ocular glaucomatous abnormalities (excavation cup-to-disc ratio > 0.3 and a visual field mean deviation < -2 dB) in patients with SSc compared with controls ($p < 0.001$). The mean IOP of the SSc patients in their study was 14.7 ± 3 mmHg, which is similar to the mean IOP found in this study (14.0 ± 3.4 mmHg).[39]

The majority of the patients in this study had satisfactory visual acuity. Cataracts were the most common cause of visual impairment and were found in 42.2% of the study population. They were presumed to be age-related and may also be present secondary to systemic corticosteroid treatment.[4] In the Framingham Eye Study, senile cataracts were seen in 15.5% of the general population, and the overall rates of cataract incidence rapidly increased with age, such that nuclear cataracts were found in 65.5% of the oldest group of study participants (75 years and older).[41]

Iris transillumination defects were found in 8.9% of the patients in our study. This was previously demonstrated as an ocular finding in SSc patients, probably as a consequence of defects in the iris pigment epithelium.[6-8]

Enophthalmos due to orbital fat atrophy was found in 3 (6.7%) patients and is probably SSc-related. Nontraumatic enophthalmos is an uncommon condition.[42] We hypothesize that it could be explained by the dermal fibrosis that occurs in SSc patients. Orbital fat atrophy is a reported complication of localized scleroderma and has also been associated with SSc.[8,43,44] Orbital varices have not been previously reported in SSc and are not directly related to SSc.

The retinal and choroidal vasculatures appear to provide an almost ideal window through which to study the generalized arteriolar and capillary pathology of SSc.[17] However, it has often been difficult to separate changes due to concomitant systemic hypertension from those that are attributable to SSc itself.[8,17,45,46] Involvement of the posterior segment of the eye is often subclinical.[6,7] Reported ophthalmoscopic findings in patients with SSc include microvascular changes, cotton-wool spots, exudates, cystoid bodies, retinal and optic nerve head edema, hemorrhages, and retinal vein and artery occlusion.[8,17,47,48,49] These abnormalities appear to be more typical of advanced SSc with renal involvement and hypertension.[8,17] Parafoveal telangiectasia has also been associated with SSc.[50,51]

In this study, 28.9% of the patients had retinal microvascular abnormalities that were indistinguishable from those related to systemic hypertension.[52]

Retinal microvascular abnormalities seem to be relatively common in the general population (2 to 14% of the nondiabetic population aged 40 years and older).[53] Several studies have shown that these abnormalities are associated with the presence and severity of hypertension.[53-55] However, these retinal signs may also be observed in people without a history of hypertension and may be related to other diseases.[53,54] A population-based study reported that arteriovenous nicking and arteriolar narrowing were independently associated with a variety of markers of inflammation and endothelial dysfunction.[55] We believe that the vasculopathy that occurs in SSc may play a role in the development of retinal vascular abnormalities and may also contribute to retinal vascular occlusions.

Recently, it has been determined that central retinal vein occlusion affects 0.8 in 1000 people. In this study, there was one case of central retinal vein occlusion among the 45 patients studied.[56]

Ushiyama et al. studied the retinal findings of 29 patients with SSc and found a higher frequency of retinal changes associated with vascular damage in SSc patients than in controls ($p = 0.01$). However, contrary to this study, they found no association between nailfold capillary changes and retinal findings.[46] In their study, nailfold capillary changes were classified into three scleroderma patterns (early, active and late), as described by Cutolo et al.[57] We grouped the scleroderma patterns into only two groups (mild versus severe) to allow statistical analysis to be conducted. The

early and active patterns were grouped together into the mild capillaroscopic findings group, whereas the late pattern corresponds to the severe capillaroscopic findings in this study.[11,57]

In patients with arterial hypertension, a reduced capillary density in different body regions has been observed. An analogous phenomenon of reduction in the nailfold area has also been observed in a group of patients with essential hypertension.[58] However, the capillaroscopic pattern in SSc is specific and is characterized by the presence of dilated and giant capillaries, hemorrhages, avascular areas, and neoangiogenesis.[11,57,59]

Several authors have noted that the nailfold capillaroscopic pattern in SSc correlates with some clinical symptoms and with the severity of the disease.[60] We found no association between the capillaroscopic pattern and either KCS or eyelid abnormalities.

Congenital hypertrophy of the retinal pigment epithelium has never been described in association with SSc. Its prevalence in the general population has been reported as 1.2%.[61] We believe this was an incidental finding.

Drusen has been reported only in aged patients with SSc.[6] In this study, it was found in two elderly patients. The prevalence of drusen increases with age and has been reported to be as high as 63% in the general population.[62]

A limitation of our study is the lack of autoantibody and capillaroscopy data for all patients. Further studies including this information should be conducted.

In conclusion, the ocular manifestations of SSc are characterized by marked heterogeneity. Eyelid skin abnormalities and KCS were the most common SSc-related ocular findings. In the posterior segment of the eye, retinal microvascular abnormalities indistinguishable from those related to systemic hypertension were the most common findings, and they seem to be associated with a severe capillaroscopic pattern. The prevalence of open-angle glaucoma was high, suggesting that SSc may be a predisposing factor for glaucoma. Patients with SSc may also develop ocular abnormalities due to systemic therapy.

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The research was approved by the review board (Comissão de Etica para Análise de Projetos de Pesquisa) of Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil. Written informed consent was obtained from all patients before surgery. The study followed the tenets of the Declaration of Helsinki.

REFERENCES

1. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, et al. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology (Oxford). 2008;47:1185-92, doi: 10.1093/rheumatology/ken179.
2. Guiducci S, Distler O, Distler JH, Matucci-Cerinic M. Mechanisms of vascular damage in SSc-implications for vascular treatment strategies. Rheumatology (Oxford). 2008;47 (Suppl 5):v18-20, doi: 10.1093/rheumatology/ken267.
3. Jinnin M. Mechanisms of skin fibrosis in systemic sclerosis. J Dermatol. 2010;37:11-25, doi: 10.1111/j.1346-8138.2009.00738.x.
4. Sakkas LI. New developments in the pathogenesis of systemic sclerosis. Autoimmunity. 2005;38:113-6, doi: 10.1080/16066350500095415.
5. Fujimoto M, Sato S. B lymphocytes and systemic sclerosis.Curr Opin Rheumatol. 2005;17:746-51, doi: 10.1097/01.bor.0000179945.73518.28.
6. West RH, Barnett AJ. Ocular involvement in scleroderma. Br J Ophthalmol. 1979;63:845-7.
7. Horan EC. Ophthalmic manifestations of progressive systemic sclerosis. Br J Ophthalmol. 1969;53:388-92.
8. Tailor R, Gupta A, Herrick A, Kwartz JOcular manifestations of scleroderma.Surv Ophthalmol. 2009;54:292-304, doi: 10.1016/j.survophthal.2008.12.007.
9. No authors listed. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23:581-90, doi: 10.1002/art.1780230510.
10. LeRoy EC, Black CM, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15:202-5.
11. Cutolo M, Pizzorni C, Secchi ME, Sulli A. Capillaroscopy. Best Pract Res Clin Rheumatol. 2008;22:1093-108, doi: 10.1016/j.berh.2008.09.001.
12. Van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol. 1969;82:10-4.
13. Homma M, Tojo T, Akizuki M, Yamagata H. Criteria for Syogren's syndrome in Japan. Scand J Rheumatol. 1986;18:26-7.
14. Manthrope R, Oxholm P, Prause JU, Schiødt M. The Copenhagen criteria for Syogren's syndrome. Scand J Rheumatol. 1986;18:19-21.
15. Dandona L, Dandona R, Srinivas M, Mandal P, John RK, McCarty CA, et al. Open-angle glaucoma in an urban population in southern India: the Andhra Pradesh eye disease study. Ophthalmology. 2000;107:1702-9, doi: 10.1016/S0161-6420(00)00275-X.
16. Dandona L, Dandona R, Mandal P, Srinivas M, John RK, McCarty CA, Rao GN. Angle-closure glaucoma in an urban population in southern India. The Andhra Pradesh eye disease study. Ophthalmology. 2000;107:1710-6, doi: 10.1016/S0161-6420(00)00274-8.
17. Reddy CV, Foster CS. Scleroderma. In: Albert DM, Jakobiec FA, eds. Principles and Practice of Ophthalmology, vol. V. Philadelphia: WB Saunders. 1994:2919-24.
18. Krieg T, Takehara K. Skin disease: a cardinal feature of systemic sclerosis. Rheumatology (Oxford). 2009;48 Suppl 3:iii14-18, doi: 10.1093/rheumatology/kep108.
19. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66:754-63, doi: 10.1136/ard.2006.062901.
20. Hamaguchi Y. Autoantibody profiles in systemic sclerosis: predictive value for clinical evaluation and prognosis.J Dermatol. 2010;37:42-53, doi: 10.1111/j.1346-8138.2009.00762.x.
21. Bell S, Krieg T, Meurer M. Antibodies to Ro/SSA detected by ELISA: correlation with clinical features in systemic scleroderma. Br J Dermatol. 1989;121:35-41, doi: 10.1111/j.1365-2133.1989.tb01397.x.
22. Alarcon-Segovia D, Ibanez G, Hermandez-Ortiz J, Velázquez-Forero F, González-Jiménez Y. Sjogren's syndrome in progressive systemic sclerosis (scleroderma). Am J Med. 1974;57:78-85.
23. Kirkham TH. Scleroderma and Sjogren's syndrome. Br J Ophthalmol. 1969;53:131-33.
24. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. Ocul Surf. 2009;7(2 Suppl):S1-S14.
25. Fotouhi A, Hashemi H, Khabazkhoob M, Mohammad K. Prevalence and risk factors of pterygium and pinguecula: the Tehran Eye Study. Eye (Lond). 2009;23:1125-9.
26. Paula JS, Thorn F, Cruz AA. Prevalence of pterygium and cataract in indigenous populations of the Brazilian Amazon rain forest. Eye (Lond). 2006;20:533-6.
27. Garrido Neto T, Garrido C, Carvalho R C, Lima H C. [Pterygium frequency study in Salvador and Manaus Hospital] Rev. Bras. Oftalmol.1996;55:683-6.
28. Hamideh F, Prete PE. Ophthalmologic manifestations of rheumatic diseases.Semin Arthritis Rheum. 2001;30:217-41, doi: 10.1053/sarh.2001.16639.
29. Akman A, Akova YA, Yücel E, Aydin P. Granulomatous anterior uveitis in a patient with CREST syndrome.Ocul Immunol Inflamm. 2000;8:201-3.
30. Courtade M, Gicquel JJ, Mercie M, Vabres B, Dighiero P. [Granulomatous uveitis and CREST syndrome: a case study] J Fr Ophtalmol. 2004;27:918-20, doi: 10.1016/S0181-5512(04)96237-7.
31. David R, Ivry M. Focal chorioretinitis and iridocyclitis associated with scleroderma. Ann Ophthalmol. 1976;8:199-202.

32. De Andrés J, García-Delpech S, Pérez VL, Díaz-Llopis M, Udaondo P, Sánchez MT, et al. Bilateral infusion pump implants as therapy for refractory corneal ulcers in a patient with CREST syndrome: an interdisciplinary approach. Arch Ophthalmol. 2008;126:964-7, doi: 10.1001/archopht.126.7.964.
33. Aleixo AL, Benchimol EI, Neves Ede S, Silva CS, Coura LC, Amendoeira MR. [Frequency of lesions suggestive of ocular toxoplasmosis among a rural population in the State of Rio de Janeiro] Rev Soc Bras Med Trop. 2009 ;42:165-9, doi: 10.1590/S0037-86822009000200014.
34. Sii F, Lee GA, Sanfilippo P, Stephensen DC. Pellucid marginal degeneration and scleroderma. Clin Exp Optom. 2004;87:180-4, doi: 10.1111/j.1444-0938.2004.tb03172.x.
35. Emre S, Kayikçioğlu O, Ateş H, Cinar E, Inceoğlu N, Yargucu F, et al. Corneal hysteresis, corneal resistance factor, and intraocular pressure measurement in patients with scleroderma using the reichert ocular response analyzer. Cornea. 2010;29:628-31.
36. Zoega GM, Fujisawa A, Sasaki H, Kubota A, Sasaki K, Kitagawa K, et al. Prevalence and risk factors for cornea guttata in the Reykjavik Eye Study. Ophthalmology. 2006;113:565-9, doi: 10.1016/j.ophtha.2005.12.014.
37. Sakata K, Sakata LM, Sakata VM, Santini C, Hopker LM, Bernardes R, et al. Prevalence of glaucoma in a South brazilian population: Projeto Glaucoma. Invest Ophthalmol Vis Sci. 2007;48:4974-9, doi: 10.1167/iovs.07-0342.
38. Yamamoto T, Maeda M, Sawada A, Sugiyama K, Taniguchi T, Kitazawa Y, et al. Prevalence of normal-tension glaucoma and primary open-angle glaucoma in patients with collagen diseases. Jpn J Ophthalmol. 1999;43:539-42.
39. Allanore Y, Parc C, Monnet D, Brézin AP, Kahan A. Increased prevalence of ocular glaucomatous abnormalities in systemic sclerosis. Ann Rheum Dis. 2004;63:1276-8, doi: 10.1136/ard.2003.013540.
40. Resch H, Garhofer G, Fuchsjäger-Mayrl G, Hommer A, Schmetterer L. Endothelial dysfunction in glaucoma. Acta Ophthalmol. 2009;87:4-12, doi: 10.1111/j.1755-3768.2007.01167.x.
41. Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, et al. The Framingham Eye Study. I. Outline and major prevalence findings. Am J Epidemiol. 1977;106:17-32.
42. Athanasiov PA, Prabhakaran VC, Selva D. Non-traumatic enophthalmos: a review. Acta Ophthalmol. 2008;86:356-64, doi: 10.1111/j.1755-3768.2007.01152.x.
43. Fernando BS, Cannon PS, Tumuluri K, Cook AE. Linear scleroderma as a rare cause of enophthalmos: a case report. J Med Case Reports. 2007;1:179, doi: 10.1186/1752-1947-1-179.
44. Kirkali PA, Kansu T, Sanac AS. Unilateral enophthalmos in systemic scleroderma. J Clin Neuroophthalmol. 1991;11:43-4.
45. Peter S, Dietrich H, Wick G. Investigations for retinopathy in an avian model for systemic sclerosis. Exp Eye Res. 2004;79:85-92, doi: 10.1016/j.exer.2004.02.012.
46. Ushiyama O, Ushiyama K, Yamada T, Koarada S, Tada Y, Suzuki N, et al. Retinal findings in systemic sclerosis: a comparison with nailfold capillaroscopic patterns. Ann Rheum Dis. 2003;62:204-7, doi: 10.1136/ard.62.3.204.
47. Raja MS, Marshall T, Burton BJ. Acute central retinal artery occlusion presenting as CREST syndrome: a case report. Cases J. 2009;2:9, doi: 10.1186/1757-1626-2-9.
48. Konuk O, Sengul O, Baran O, Tiftikcioglu Y, Gokhan G, Berati H. Ocular ischemic syndrome presenting as central retinal artery occlusion in scleroderma: brief report. Retina. 2006;26:102-4, doi: 10.1097/00006982-200601000-00017.
49. Minasian M, Stanford M, Graham E, Denton CP, Black C. Bilateral ischaemic retinal vasculopathy in scleroderma. Br J Ophthalmol. 2005;89:1064-5.
50. Proctor B, Chang T, Hay D. Parafoveal telangiectasia in association with CREST syndrome. Arch Ophthalmol. 1998;116:814-5.
51. Huerva V, Sánchez MC. Juxtafoveolar telangiectasis associated with CREST syndrome. Ocul Immunol Inflamm. 2008;16:195-7, doi: 10.1080/09273940802217867.
52. Wong TY, Mitchell P. The eye in hypertension. Lancet. 2007;369:425-35, doi: 10.1016/S0140-6736(07)60198-6.
53. Klein R, Klein BEK, Moss SE, Wang Q. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. Arch Ophthalmol. 1994;112:92–8.
54. Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. Arch Ophthalmol. 1998;116:83-9.
55. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, et al. International Eye Disease Consortium. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology. 2010;117:313-319.e1, doi: 10.1016/j.ophtha.2009.07.017.
56. Klein R, Sharrett AR, Klein BE, Chambless LE, Cooper LS, Hubbard LD, et al. Are retinal arteriolar abnormalities related to atherosclerosis? The Atherosclerosis Risk in Communities Study. Arterioscler Thromb Vasc Biol. 2000;20:1644–50.
57. Cutolo M, Pizzorni C, Sulli A. Capillaroscopy. Best Pract Res Clin Rheumatol. 2005;19:437-52, doi: 10.1016/j.berh.2005.01.001.
58. Gasser P, Bühler FR. Nailfold microcirculation in normotensive and essential hypertensive subjects, as assessed by video-microscopy. J Hypertens. 1992;10:83-6, doi: 10.1097/00004872-199201000-00013.
59. Lambova SN, Müller-Ladner U. The specificity of capillaroscopic pattern in connective autoimmune diseases. A comparison with microvascular changes in diseases of social importance: arterial hypertension and diabetes mellitus. Mod Rheumatol. 2009;19:600-5, doi: 10.1007/s10165-009-0221-x.
60. Cutolo M, Pizzorni C, Sulli A. Nailfold video-capillaroscopy in systemic sclerosis. Z Rheumatol. 2004;63:457-62, doi: 10.1007/s00393-004-0673-5.
61. Coleman P, Barnard NA. Congenital hypertrophy of the retinal pigment epithelium: prevalence and ocular features in the optometric population. Ophthalmic Physiol Opt. 2007;27:547-55, doi: 10.1111/j.1475-1313.2007.00513.x.
62. Klein R, Cruickshanks KJ, Nash SD, Krantz EM, Javier Nieto F, Huang GH, et al. The prevalence of age-related macular degeneration and associated risk factors. Arch Ophthalmol. 2010;128:750-8, doi: 10.1001/archophthalmol.2010.92.