Ocular surface alterations in patients hospitalized for SARS-CoV-2

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BACKGROUND. SARS-Cov-2 is a single-stranded RNA virus belonging to the family Coronaviridae. It is the causative agent of COVID-19 disease and responsible for the current pandemic that affects more than 30 million people worldwide (1, 2). Although COVID-19 is identified as a systemic disease with mainly pulmonary and respiratory transmission, various studies present the ocular surface as a possible route of infection and a potential infectious target (6,7). To better understand this type of extrapulmonary manifestations and contribute to the development of better diagnostic approaches and therapeutic, in this study we try to describe some alterations of the ocular surface in patients hospitalized for SARS-CoV-2 in the COVID-19 isolation area of the Hospital de Especialidades Centro Médico Nacional Siglo XXI in Mexico City. And we found that most of the patients had conjunctival rather than corneal involvement, which corresponds to the few reported symptoms. Subconjunctival microbleeds were the predominant clinical sign, which is not reported in the international literature, and we can infer that it is related to the microvascular damage caused by the virus and / or to the anticoagulant treatment that patients with COVID-19 undergo. Likewise, no relationship was found between the days of hospital stay and the degree of damage to the ocular surface according to Oxford classification or the presence or absence of subconjunctival microbleeds. Similarly, no significant differences were found between the type of supplemental oxygen used and the degree of damage to the ocular surface by Oxford and the presence or absence of subconjunctival microbleeds.

KEY WORDS: SARS-COV-2, Ophtalmic changes in COVID.

Introduction

SARS-Cov-2 is a single-stranded RNA virus belonging to the family Coronaviridae and the order Nidovirales. It is the causative agent of COVID-19 disease and responsible for the current pandemic that affects more than 30 million people worldwide (1, 2). It was first isolated in Hubei, China on January 7, 2020 (3) and with the publication of its genetic sequence it was postulated that its evolutionary origin was recent and that the bat was the probable primary source (4). There are currently more than 40 million confirmed cases and about 1,200,000 deaths worldwide (5). In Mexico, the first case was reported on February 28, 2020, and there are currently about 2,740,000 cases with 238,000 deaths (5). Although COVID-19 is identified as a systemic disease with mainly pulmonary and respiratory transmission, various studies present the ocular surface as a possible route of infection and a potential infectious target (6,7).

Transmission and infection of SARS-CoV-2 by ocular route

Anatomically, the ocular surface represents a vulnerable area since it is exposed to external agents present in the air and with potential risk to direct contact through fomites (8). Of the two components of the ocular surface: the corneal epithelium and the conjunctival epithelium, the latter has angiotensin-2-converting enzyme receptors (ACE-2) specific for SARS-CoV-2, although in much smaller quantities than the pulmonary epithelium (9). This fact, coupled with the contiguity of the eye with the nasolacrimal

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Variable	N= 100
Male. No., (%)	60, (60)
Age, mean (SD) years	54.84, (14.93)
Pathological personal history. No., (%)	71, (71)
Ophthalmological History No., (%)	53, (53)
Days of Hospital Stay, mean (SD)	4.3, (2.6)
Supplemental Oxygen. Nasal cannulas. No., (%)	73, (73)

Table 1. Demographic characteristics and antecedents of the study population. 100 patients hospitalized for SARS-CoV-2 in UMAE HE CMN Siglo XXI. No= Number; SD= Standard deviation; SPSS V.24.0 software was used.

duct and the upper respiratory tract, makes the ocular surface an important means of contagion and a possible target of infection (10,11). To date, however, reported cases of SARS-Cov-2 viral conjunctivitis and cases of conjunctivitis with positive PCR in tears or conjunctival secretions are very rare (12,13).

Ocular surface alterations by SARS-CoV2

Among the main ocular pathological changes described in COVID-19 are conjunctival hyperemia, conjunctival follicles, lacrimation, corneal de-epithelialization, alteration of the tear film and secretion (11-13). The little reported evidence of ocular manifestations attributable to SARS-Cov-2 may be due to the insufficient opportunity for ophthalmological examination in isolated patients, the self-limitation of the ocular pictures or the little importance that is given to the ocular surface when it could provide us with information very valuable (14,15).

Ocular Surface Damage by SARS-CoV-2

Some authors postulate that, although there is evidence of ocular involvement in SARS-CoV-2 infection, cases are rare because the expression of ACE2 receptors is much lower in the conjunctiva than in other tissues such as the pulmonary or renal epithelium. Likewise, the affinity of the virus to the conjunctival receptor is lower due to the action of lactoferrin and IgA present in the tear (1). However, ACE2 receptors have been detected in the retina, and in the retinal pigment epithelium, so further studies should be carried out (2).

Chen et al., presented a case report of a 30-year-old patient with evidence of bilateral follicular conjunctivitis with a positive test for SARS-Cov-2 in conjunctival secretion, 13 days after the onset of respiratory symptoms. The clinical characteristics

Symptoms	
Variable	Patients, n= 100
Eye pain. No., (%)	6, (6)
Pink eye. No., (%)	4, (4)
Secretion. No., (%)	4, (4)
Tearing. No., (%)	1, (1)
Clinical signs	
Variable	Eyes, n= 200
Micro-subconjunctival Hemorrhages. No., (%)	170, (85)
Conjunctival hyperemia. No., (%)	146, (73)
Conjunctival Folds. No., (%)	134, (67)
Ciliary Injection. No., (%)	22, (11)
Mucous secretion. No., (%)	20, (10)
Chemosis. No., (%)	18, (9)
Follicles. No., (%)	2, (1)
Oxford Classification	
Grade	Eyes, n=200
0 No., (%)	76, (38)
I No., (%)	86, (43)
II No., (%)	38, (19)

Table 2. Symptoms, Clinical Manifestations and Oxford Classification of 100 patients (200 eyes) hospitalized for SARS-COV-2 at UMAE HE CMN Siglo XXI. No= Number; SD= Standar deviation; SPSS V.24.0 software was used.

found were bilateral blurred vision, foreign body sensation, conjunctival injection, lacrimation and palpebral conjunctival follicles, this associated with palpable pre-atrial lymph nodes (22).

Although the most appropriate way to observe these changes in the ocular surface is using a slit lamp, in special situations, the evaluation can be performed macroscopically and with the help of special stains that aid to highlight the pathological changes. One of the most used dyes is fluorescein, which is a non-irritating substance that with blue illumination allows us to observe areas without epithelium on the ocular surface and weak intercellular junctions (6).

According to various studies, the incidence of SARS-CoV-2 ocular infections is extremely low in the general population, however, it represents a potential transmission route in health personnel, therefore, the use of eye protection should be widely used by all professionals who treat patients with COVID or in potentially exposed areas (1,2).

In this way, the objective of this study is to know the alterations of the ocular surface in patients hospitalized for SARS-CoV-2 in the Mexican population to better understand this type of extrapulmonary manifestations and contribute to the development of better diagnostic approaches and therapeutic.

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Variable	1 to 6 days (n=86)	7 to 14 days (n=14)	P value
Oxford grade 0. No., (%)	33, (38.4)	7, (50)	
Oxford grade I. No., (%)	39, (45.3)	4, (28.6)	0.671
Oxford grade II. No., (%)	14, (16.3)	3, (21.4)	
Reservoir Mask. No., (%)	18, (20.9)	9, (64.3)	0.680
Nasal Tips. No., (%)	68, (79.1)	5, (35.7)	
Micro-subconjunctival Hemorrhages. No., (%)	70, (81.4)	10, (71.4)	0.390

Table 3. Relationship between the days of hospital stay by groups of 1 to 6 days and 7 to 14 days, and the presence of damage to the ocular surface by Oxford, type of use of supplemental oxygen (reservoir mask or nasal tips) or presence of subconjunctival microhemorrhages in 100 patients hospitalized for SARS-CoV-2 in UMAE HE CMN Siglo XXI.No= Number; SPSS V.24.0 software was used to calculate the Mann-Whitney U test.

Methods

A descriptive, cross-sectional, prospective and observational study was carried out from April 23 to August 20, 2020. Patients older than 18 years of age, of indistinct sex, with a diagnosis of SARS-CoV-2 pneumonia with a positive PCR test and without ventilatory mechanical support, hospitalized in the COVID-19 isolation area of the Hospital de Especialidades Centro Médico Nacional Siglo XXI, were selected.

A randomized sampling of non-consecutive cases was carried out and the patients who met the selection criteria received a complete ophthalmological medical history. A questionnaire was carried out that included the days of hospital stay at the time of the review, the type of supplemental oxygen used at that time and the presence or absence of ocular symptoms from seven days prior to the onset of respiratory symptoms.

A macroscopic ophthalmological examination was performed with the application of a 1 mg BIO GLO ™ sodium fluorescein strip with previous instillation of a drop of 5 mg / ml Ponti Ofteno ® tetracaine in each eye and an ultraviolet light filter; anterior segment photographs were taken with a 24 megapixels resolution Nikon® D3200 reflex camera. Afterwards, the photos were analyzed in which the presence of clinical signs and tear meniscus size was considered. Oxford classification was used to evaluate the damage degree to the ocular surface. For continuous quantitative variables, the measures of central tendency and standard deviation were used as dispersion parameters. Simple percentages and frequencies were used for qualitative variables. Nonparametric Mann-Whitney U tests were used for data analysis and a P value <0.05 was considered significant in rejecting the null hypothesis in all tests.

This study was based on the current ethical guidelines of current international guidelines, with the considerations issued in the Nuremberg Code, the Declaration of Helsinki and all its amendments, as well as the international guidelines for medical research with human beings, adopted by the WHO and the Council of International Organizations for Research with Human Beings. In Mexico, it complied with the provisions of the General Health Law on Research for Health and Protection of Personal Data.

Results

Anterior segment photographs were obtained from 100 patients hospitalized for SARS-CoV-2, from April 23 to August 12, 2020. A total of 200 eyes were evaluated. Within the demographic characteristics, the mean age was 54.84 years (SD ± 14.93, median 56.5, mode 80, minimum 21, maximum 80); the male sex was the most frequent (n = 60, 60%), compared to the female (n = 40, 40%). (Table 1).

The most frequent comorbidity was hypertension (n = 45, 45%), followed by diabetes mellitus (n = 37, 37%) and obesity (n = 19, 19%).

The average days of hospital stay at the time of the evaluation was 4.3 days (SD ± 2.6, median 4, mode 2, minimum 1, maximum 14). Regarding the use of supplemental oxygen, 73% of the patients used nasal cannulas (n = 73) and 27% (n = 27), a mask with a reservoir bag at the time of the study.

Within the ophthalmological history, the most frequent was ametropia (n = 47, 47%), followed by cataract (n = 12, 12%) and previous surgery (n = 11, 11%).

Of the 100 patients analyzed, 85% (n = 85) were ophthalmologically asymptomatic from 7 days before hospitalization until the time of the study. 15% (n = 15) of the patients had symptoms such as eye pain or burning (n = 6, 6%), pink eye (n = 4, 4%), discharge (n = 4, 4%) and lacrimation (n = 1.1%).

Within the analysis of the ocular surface of the 200 eyes included in the sample, 95% (n = 190) presented some alteration in the ocular surface. The most frequently found clinical signs were subconjunctival microbleeds (n = 160, 80%), (graph 1); conjunctival hyperemia (n = 146, 73%); conjunctival folds (n = 134, 67%); ciliary injection (n = 22, 11%); mucous discharge (n = 20, 10%); chemosis (n = 18.9%) and follicles (n = 2.1%).

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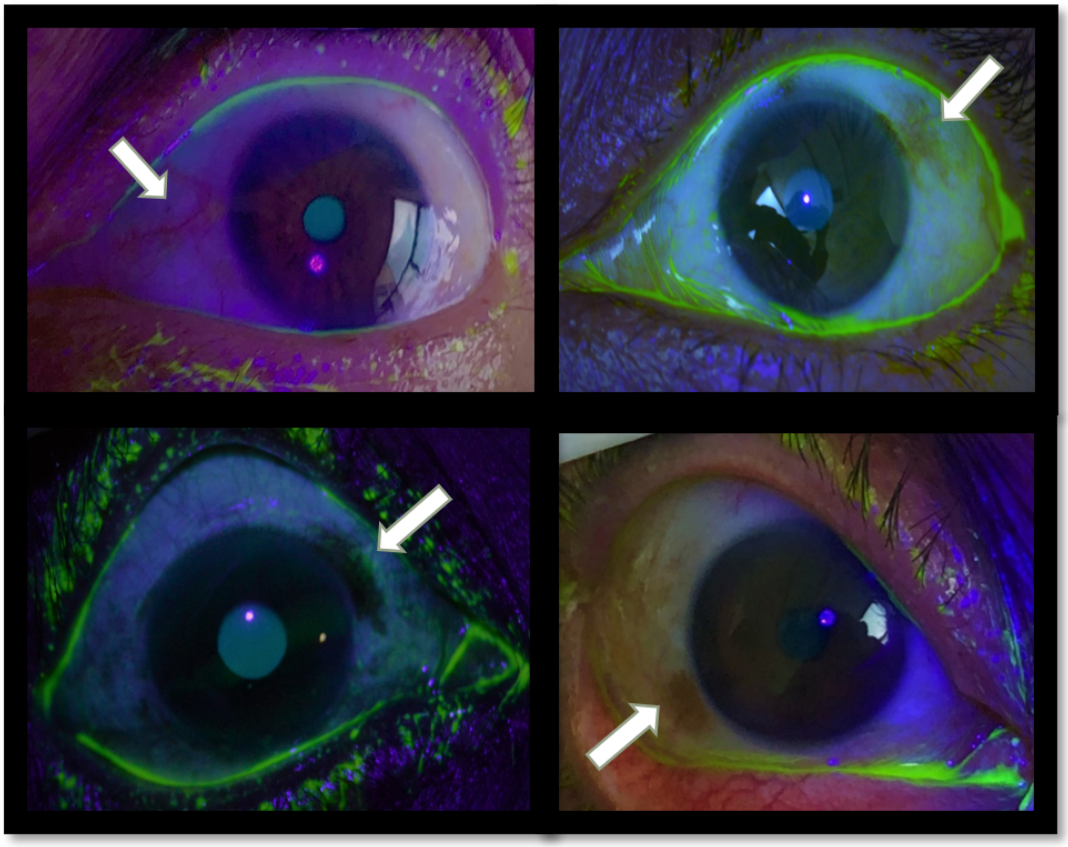

Figure 1. Subconjunctival micro hemorrhages. Multiple punctate subconjunctival hemorrhages are observed, predominantly in the nasal or temporal sector. The arrow points to the site of the microbleed.

The tear film integrity evaluation was performed by measuring the tear meniscus, finding that the majority (n = 178, 78%) presented tear meniscus > 1 millimeter.

For the general evaluation of the ocular surface, the Oxford clinical classification was used (Table 3). 43% of the eyes analyzed (n = 86) were classified as grade I (figure 5); 38% (n = 76) grade 0 and the remaining 17% (n = 34) as Oxford grade II. (Table 2).

The patients were grouped according to the days of hospital stay. From 1 to 6 days and from 7 to more days. Descriptive analysis of the Oxford classification, the type of supplemental oxygen used and the presence of subconjunctival microbleeds was carried out.

A non-parametric test was performed to determine the difference between the Oxford classification grades and the presence or absence of subconjunctival microbleeds according to the groups of days of hospital stay (group 1: 1-6 days, group 2: 7 or more days). The Oxford classification did not show significant differences according to the days of hospital stay (Mann-Whitney U test, P = 0.671). The presence or absence of bleeding did not show significant differences according to the days of hospital stay (Mann-Whitney U test, P = 0.390).

A non-parametric test was performed to determine the difference between the Oxford classification grades and the presence or absence of microbleeds according to the type of supplemental oxygen used (nasal tips or reservoir mask). The Oxford classification did not show significant differences according to the type of supplemental oxygen used (Mann-Whitney U test, P = 0.680). The presence or absence of bleeding did not show significant differences according to the type of supplemental oxygen used (Mann-Whitney U test, P = 0.370). (Table 3)

Discussion

The age and sex distribution of the patients analyzed in this study coincide with the international literature, with an average age between the fifth and sixth decade of life and a predominance of males (11). According to Xia J, Zhang X and collaborators (12,13), 1-5% of the patients who evaluated presented "ocular discomfort" at the time of their review, which contrasts with 15% of the patients who presented some symptom ophthalmology in the present study, this is due to the fact that our questioning was conducted up to 7 days prior to the appearance of any respiratory symptoms.

As in the international literature, the main symptoms referred to were burning or "ocular discomfort, pink eye and discharge. With little or no alteration of visual acuity, which coincides with the present study. Likewise, the main ophthalmological signs found in this study: conjunctival hyperemia, discharge and lacrimation correspond to the literature consulted. However, the predominant signs found in

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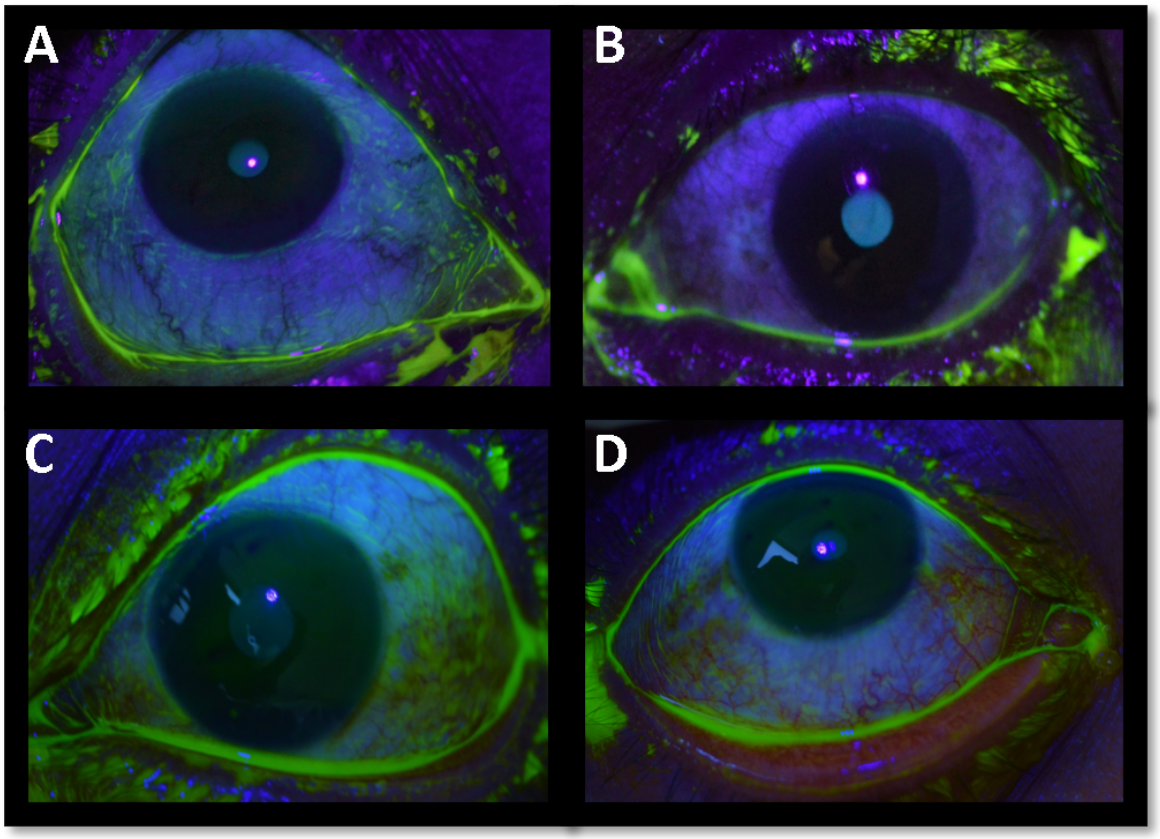

Figure 2. Conjunctival hyperemia. The four images show an engorgement of the subconjunctival vessels that produces generalized redness (A and B) or sectorial (C and D).

this evaluation, subconjunctival microbleeds and conjunctival folds, are not mentioned in the international literature. Various factors can influence the appearance of these signs, such as the microvascular endothelial inflammatory process caused by the SARS-CoV-2 virus, the anticoagulant treatment to which the patients were subjected at the time of the review, or the use of supplemental oxygen. However, more observations are required to identify the real cause of these manifestations.

Within what was evaluated in the present study, no significant differences were found between the days of hospital stay and the degree of damage to the ocular surface classified by Oxford or the presence or absence of subconjunctival microbleeds. Likewise, no statistically significant difference was found between the type of supplemental oxygen used and the degree of damage to the ocular surface classified by Oxford or the presence or absence of subconjunctival microbleeds.

Conclusion

Most of the patients had conjunctival rather than corneal involvement, which corresponds to the few reported symptoms. Subconjunctival microbleeds were the predominant clinical sign, which is not reported in the international literature, and we can infer that it is related to the microvascular damage caused by the virus and / or to the anticoagulant treatment that patients with COVID-19 undergo.

Likewise, no relationship was found between the days of hospital stay and the degree of damage to the ocular surface according to Oxford classification or the presence or absence of subconjunctival microbleeds.

Similarly, no significant differences were found between the type of supplemental oxygen used and the degree of damage to the ocular surface by Oxford and the presence or absence of subconjunctival microbleeds.

Conflicts of interests

The authors declares that there is no conflict of interest.

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