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Can the Use of B-Mode Ultrasonography Assess Ocular Changes in Patients with Axial Spondyloarthritis?

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Abstract

Objectives: To evaluate, through ocular B-mode ultrasonography, the presence of vitritis and its complications in patients with radiographic and non-radiographic axial spondyloarthritis, comparing with clinical, laboratory and ophthalmological examination aspects.

Methods: Observational and cross-sectional study, in 30 patients selected from the Rheumatology outpatient clinic of the PUC Hospital in Campinas, SP, Brazil, who met the Assessment of Spondyloarthritis International Society criteria, from August to December 2021, was evaluated 60 eyes using high-frequency ultrasound, semi-quantitatively classifying vitritis in 0 to 3 degrees, that is, absence, mild, moderate and severe disorder, respectively.

Results: Patients with a mean age of 46.3 ± 13 years, male (63.3%), white (66.7%), diagnosed with radiographic axial spondyloarthritis (80.0%) and with disease duration of more than 5 years (63.3%). Ocular ultrasound showed vitritis in 62.5%, but without statistically significant difference. There was a statistically significant difference in the presence of cataracts and optic nerve thickening with p=0.037 and p=0.007, respectively.

Conclusion: We observed a significant percentage of chronic inflammatory processes in the vitreous humor on ultrasound in patients with spondyloarthritis in inflammatory activity, as well as some complications of chronic uveal inflammatory process, characterized by cataracts and optic nerve enlargement. In the future, B-mode ultrasound may be an adjuvant tool in the ophthalmological evaluation of patients with axial spondyloarthritis and ocular alterations.

Keywords: Vitritis; Uveitis; B-mode ultrasound; Spondylarthritis

Introduction

Uveitis is defined as an inflammation of the iris, ciliary body, vitreous, retina and/or choroid [1,2]. Incidence is 17-52/100.000 people-years and prevalence is 38-284/100,000 people-years [3-6]. About 60 causes of uveitis have been described and can be classified into 5 groups: single ophthalmological causes, infectious causes, inflammatory diseases, masked syndromes and drug-related uveitis [7,8]. The inflammatory diseases include spondyloarthritis [7,8]. Ankylosing spondylitis is the prototype of this group of diseases [9], whose pathophysiological basis is enthesitis [10,11]. The enthesis is defined as the soft tissue site where the ligament, tendon or joint capsule are anchored to the bone; on the other hand, the anterior chamber of the eye contains mini-entheses (ciliary body), which explains the inflammation of this structure in spondyloarthritis [11]. During embryogenesis the vitreous humor is formed by cells in the unpigmented portion of the ciliary body, the vitreous humor is derived from embryonic mesenchymal cells, which degenerate after birth [12].

The prevalence of acute anterior uveitis among patients with spondyloarthritis is approximately 25.8%, with a significant association with time of disease diagnosis; in patients with disease duration of less than 10 years it is around 17.4%; in patients with over 20 years disease duration, it is around 38.5% [13]. Clinical complaints of uveitis are photophobia, visual loss, pain, and ocular hyperemia. Clinical examination with slit-lamp biomicroscopy is the gold standard for diagnosis [13,14]. B-mode ultrasound is a quick, safe, easy-to-access test available at bedside that can provide useful information for confirming uveitis, as described by Doro et al when performing ocular ultrasound in 7 patients with a clinical diagnosis of intermediate uveitis and concluded that this exam is of special value in patients with small pupils and dense vitritis [15].

Ocular ultrasound is a non-invasive examination with a dynamic approach to different intraocular structures, allowing the monitoring of these structures, especially when there is difficulty in observation due to loss of transparency in the optical parts (cornea, lens and vitreous body). Ultrasonography also evaluates posterior vitreous detachment, macular edema, choroidal detachment, scleral thickening and retinal detachment [16]. Thus, our objective was to evaluate the ocular inflammatory process and its complications using B-mode ultrasonography in patients with axial spondyloarthritis and compare these findings with clinical laboratory aspects.

Case Presentation

Methods

A cross-sectional observational study with clinical and ophthalmological evaluation and high-frequency B-mode ultrasound eye examination; a total of 30 patients with radiographic and non-radiographic axial spondyloarthritis who were treated at the Rheumatology outpatient clinic of the PUC-Campinas Hospital during the months of August to December 2021 were selected. The patients underwent an ophthalmological examination by a single ophthalmologist specializing in uveitis, at the Ophthalmology Service of the PUC Hospital, Campinas, SP, Brazil.

Ophthalmologic evaluation was performed by anterior and fundus biomicroscopy, using a slit lamp. To standardize the assessment, the description of the anatomical site and uveitis intensity were based on the classification of the SUN group-Standardization of Uveitis Nomenclature [17].

Patients were evaluated by a single rheumatologist according to the BASDAI indices (Bath Ankylosing Spondylitis Disease Activity Index) [18,19] and ASDAS (Ankylosing Spondylitis Disease Activity Score) [20,21] of disease activity, in addition to collecting demographic data (race, height, weight, age, gender, profession, education), type of disease involvement (ankylosis on radiography), time of diagnosis, treatment used, investigation of comorbidities by direct questioning or searching the medical records (systemic arterial hypertension, diabetes mellitus, dyslipidemia, hypothyroidism, sarcoidosis, amyloidosis, syphilis, Lyme disease, tuberculosis, toxoplasmosis, osteoarthritis, gout), questioning about uveitis clinical signs and symptoms [17], collection of laboratory tests performed reported in medical records (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting blood glucose, glycosylated hemoglobin, total cholesterol and fractions, triglycerides, uric acid, HLA-B27), changes in imaging tests (MRI or pelvic X-ray).

The 30 patients and 60 eyes underwent B-mode ocular ultrasound examination, performed by a single rheumatologist with fifteen years of experience in this imaging method. The examination was performed using a MyLab 50 Gold ultrasound model (EsaoteSpA, São Paulo, Brazil) with a high-frequency linear probe, ranging from 10-18 MHz, with 12 MHz being used to assess the echotexture using the gray scale. Each patient was placed in a supine position. The patient maintained his/her eyes closed. For a better visualization of the ocular structures, an large amount of water-based gel was applied on the eyelids, without the linear probe pressing the ocular structures (avoiding the collapse of the anterior chamber) [22-24]. The ocular ultrasonographic evaluation followed a predetermined sequence, with an average duration of 5 minutes, to assess the entire ocular integrity. First, a topographical assessment was carried out to locate and determine the shape of any abnormality. Afterwards, the quantitative evaluation of the vitreous echoes was carried out and finally the kinetic evaluation, which determines the mobility of the structures, either pathological or not. The high gain in B-mode, with the maximum change, by decreasing the "dynamic range", is initially used with the aim of visualizing the vitreous cavity, being reduced as needed to assess the retina, the choroid and solid lesions. Obtaining the images must follow the protocol that requires images in the axial section of the entire eyeball, from the upper to the lower pole, and sagittal images from the temporal to nasal portion. During the examination, patients were asked to move their eyes mid-laterally and vertically, with the probe positioned longitudinally and transversely to obtain oblique and dynamic images [25]. The classification of vitreous echoes intensity is not yet standardized. Thus, making an analogy with the degrees of joint effusion seen by ultrasound [26], the following classification was created (Figure 1):

•**Grade 0:** No change in vitreous humor.

•**Grade 1:** Discreet presence of vitreous echoes concentrically or diffusely throughout the area of the vitreous humor, corresponding to ≤ 25% of the area.

•**Grade 2:** Moderate presence of vitreous echoes concentrically or diffusely throughout the area of the vitreous humor, corresponding to ≥ 50% of the area.

•**Grade 3:** Intense presence of vitreous echoes concentrically or diffusely throughout the area of the vitreous humor, corresponding to ≥ 75% of the area.

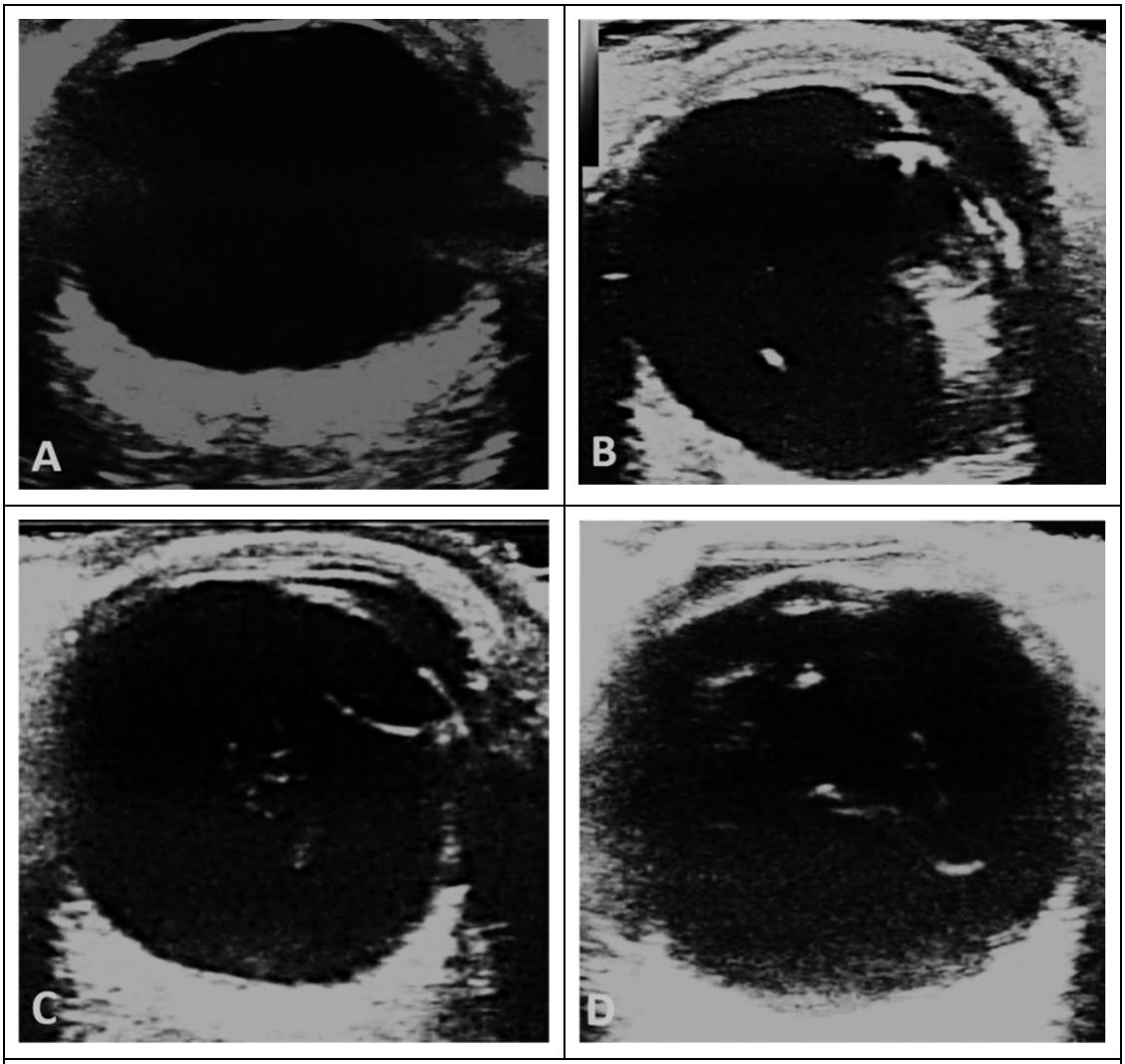

Figure 1: Intermediate uveitis in patients with axial spondyloarthritis: **(A):** Grade 0 vitritis; **(B):** Grade 1 vitreitis; **(C):** Grade 2 vitreitis; **(D):** Grade 3 vitreitis. **Note:** B-mode ultrasound images.

The optic nerve sheath was measured by ocular ultrasound examination, 3 mm behind the eyeball. The section showing the maximum transverse diameter of the eyeball was frozen and the sheath diameter was measured. The cut-off value used to consider optic nerve thickening was equal to or greater than 5 mm [27]. All still and dynamic images were recorded on external hardware.

Each professional did not have access to the information collected by the other professionals.

The study was approved by the ethics committee of the Pontifícia Universidade Católica de Campinas Hospital, under opinion number 5.156.121.

For the characterization of the sample, descriptive analyses of frequencies (absolute and relative) were performed for categorical variables, mean and standard deviation (SD) for the quantitative variables with approximately normal and median distribution and interquartile range (IQR), first quartile (Q1) and third quartile (Q3) for quantitative variables with asymmetric distribution.

Sociodemographic and clinical variables were compared according to the clinical outcome (with or without uveitis), according to the ultrasound classification. The t-Student test was used to compare the age variable and the Mann-Whitney test for the ASDAS, BASDAI, CRP and ESR variables when quantitatively evaluated. The other categorical variables were compared using the chi-square test or Fisher's exact test. Data were recorded in password-protected Excel spreadsheets and all statistical analyses were performed using the SAS Studio statistical package version 3.8. The level of statistical significance considered was 5% ($p < 0.05$).

Results:

The mean age was 46.3 (±13) years; most patients were male (63.3%), white (66.7%), had a disease duration of more than 5 years (63.3%), radiographic disease features (80%) and were active according to ASDAS (85.7%) (Table 1).

Table 1: Sociodemographic and Clinical Characteristics of the Sample.

Characteristics	**n**	**Values (mean/%)**
Age (years)	30	46.3 (±13.0)
Gender		
Male	19	63.3
Female	11	36.7
Race/Color		
White	20	66.7
Brown	8	26.7
Black	2	6.7
Type of involvement		
Radiographic SpA	24	80.0
Non-radiographic SpA	6	20.0
Time of illness (in years)		
0 to 5	11	36.7
6 to 10	4	13.3
>10	15	50.0
ASDAS	28	2.6 (1.7-3.3)
Inactive disease (<1,3)	4	14.3
Moderate disease activity (≥1.3 a <2.1)	7	25.0
High disease activity (≥2.1 to ≤3.5)	11	39.3
Very high disease activity (>3.5)	6	21.4
BASDAI	30	3.5 (1.6-7.1)
Inactive disease (≤4)	17	56.7
Active disease (>4)	13	43.3
CRP (mg/dL)	28	0.6 (0.2-1.1)

ESR (mm)	28	13.0 (8.0-26.0)
HLA-B27		
Positive	15	50.0
Negative	7	23.3
Not performed	8	26.7

Values are mean ± SD, median (IQR) or n (%).

IQR: Interquartile range; **SpA:** Spondyloarthropathies; **ASDAS:** Ankylosing Spondylitis Disease Activity Score; **BASDAI:** Bath Ankylosing Spondylitis Disease Activity Index **CRP:** C-reactive protein; **ESR:** Erythrocyte Sedimentation Rate; **HLA-B27:** B27 Human Leukocyte Antigen.

When asked about ocular symptoms, about 33% of patients had some ocular symptom (hyperemia, pain or feeling of sand in the eyes) and 50% of patients reported worsening of the vision. As for comorbidities, 40% had systemic arterial hypertension, 27% had osteoarthritis, 17% had a diagnosis of diabetes mellitus and dyslipidemia.

In the ophthalmological evaluation, most patients did not have detected uveitis (90% in the right eye and 80% in the left eye). Most affected patients had mild anterior uveitis, and only one patient had panuveitis. No changes were detected for diabetic or hypertensive retinopathy or infectious processes.

Ocular ultrasound did not detect anterior uveitis in any patient evaluated but found vitritis in more than half of the eyes evaluated (53.3% right eye/60% left eye). Among the patients who had vitreitis, most were vitreitis grade 2 (moderate) or 3 (severe) of echo intensity, that is, with greater ocular inflammation. The ultrasound evaluation revealed that 26.67% of the evaluated eyes had cataract (Table 2).

Table 2: Ultrasound Assessment.

Characteristics	**RE n (%)**	**LE n (%)**
Vitreitis	16 (53.3)	18 (60.0)
Echoes Intensity		
Absent	14 (46.7)	12 (40.0)
Light	8 (26.7)	6 (20.0)
Moderate	7 (23.3)	11(36.7)
Important	1 (3.3)	1 (3.3)
Posterior vitreous displacement	0 (0.0)	2 (6.7)
Vitreous beams	3 (10.0)	5(16.7)
Cataract	4 (13.3)	4(13.3)
Optic nerve		
> 5 mm	9 (31.1)	14(50.0)
≤ 5 mm	19 (67.9)	14(50.0)

RE/LE: Right eye/Left eye.

About 62.5% of the patients who presented uveitis on ocular ultrasound had radiographic evidence of the disease (Radiographic Axial Spondyloarthritis). Patients with disease duration of 6 to 10 years, high ASDAS and BASDAI activity index, laboratory findings with increased CRP, positive HLA-B27 and ocular symptoms had greater detection of vitritis by ultrasound, although without statistical significance (p>0 .05).

In our sample, there was a statistically significant difference in the presence of cataract, which can be considered a complication of the chronic uveal process detected by ultrasound in young patients with spondyloarthritis (p=0.037) (Figure 2) (Table 3).

Among the patients who had increased thickness of the optic nerve, 78.3% had vitritis, suggesting that the chronic inflammatory process can cause optic nerve thickening detected by ultrasound (Figure 3) (Table 3).

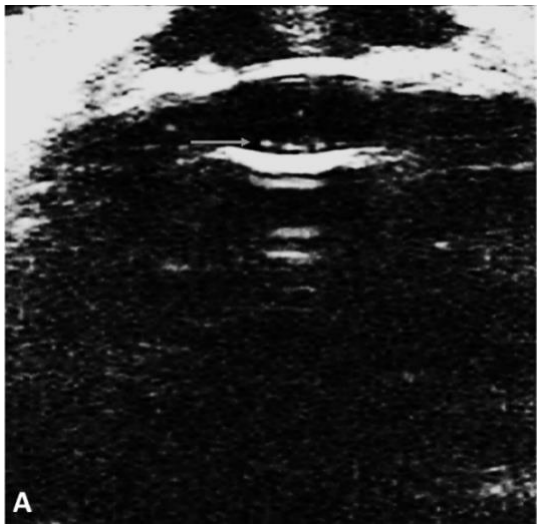

Figure 2: Male patient, 35 years old, with axial spondyloarthritis: **(A):** Lens hyperechoic image, characterizing the presence of cataract (arrow).

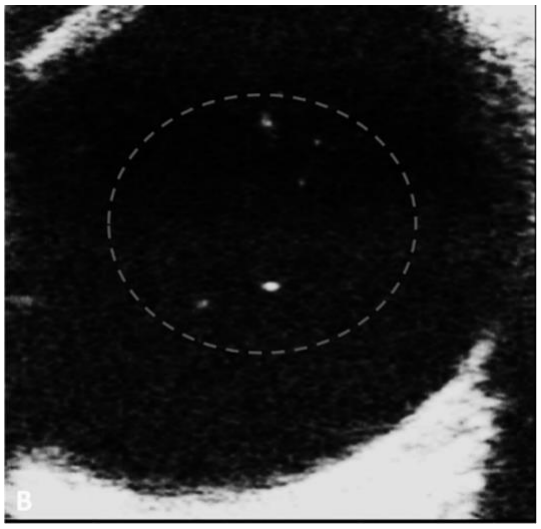

Figure 2(B): Vitreous echoes, characterizing uveitis (circle).

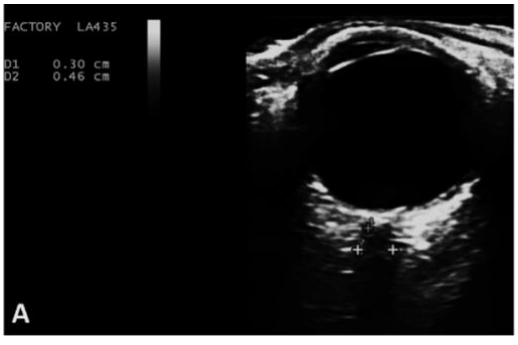

Figure 3: B-mode ultrasound images of the optic nerve sheath measurement: **(A):** Normal measurement (0.46cm).

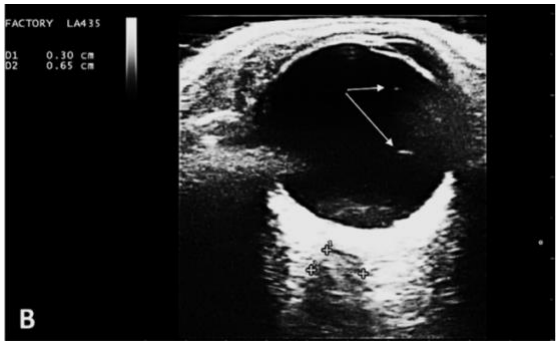

Figure 3(B): Thickening of the optic nerve in a patient with vitreous echoes, characterizing uveitis (0.65cm) (arrows).

Table 3: Ophthalmological Evaluation, According to Ultrasound Classification.

Characteristics	**With uveitis (n=34)**		**No uveitis (n=26)**		**p-value**
	n	**%**	**n**	**%**	
Uveitis (ophthalmological evaluation)	6	66.7	3	33.3	0.7186[a]
Anatomical Classification of Uveitis					
Absent	28	54.9	23	45.1	0.0702[a]
Previous	6	85.7	1	14.3	
Panuveitis	0	0.0	2	100.0	
Vitreous detachment	19	59.4	13	40.6	0.6508[b]
Synechiae	4	66.7	2	33.3	0.6892[a]
Cataract	10	83.3	2	16.7	0.0371[b]
Complications[*]					
0	11	45.8	13	54.2	0.2949[b]
1	13	59.1	9	40.9	
2	10	71.4	4	28.6	
Optic nerve (>5 mm)	18	78.3	5	21.7	0.0077[b]

[*]The complications considered were: Vitreous detachment, Synechiae, Cataract, Retinal detachment, Hemorrhage and Glaucoma, the last 3 of which did not occur in the evaluated patients.

[a]Fisher's Exact Test; [b]Chi-square Test.

Discussion

Although the uveitis characterized in axial spondyloarthritis whether it is acute, unilateral or recurrent [28], there are also reports that ocular inflammation can become chronic [29]. The accumulation of inflammatory debris in the vitreous gel as a consequence of chronic iridocyclitis can lead to vision decrease. Vitreous opacification in recurrent iridocyclitis seems to occur as a consequence of the subsequent overflow of inflammatory cells, fibrin and other materials from the ciliary body into the vitreous [29]; in addition, embryology demonstrates that there is production of vitreous humor and aqueous humor by the ciliary body [30].

There are several studies that demonstrate vitritis in patients with axial spondyloarthritis, with prevalence varying between 40.1% and 93.1% [31-33]; such reports may explain the presence of vitreitis evidenced by ocular ultrasound in a large part of our sample (56.7%).

Spondyloarthritis has systemic manifestations; the pathophysiological process of inflammation characterizes findings of inflammatory cells and interleukins in synovitis, also seen as these components located in the acute inflammatory process of the aqueous humor and also when chronic in the vitreous humor, demonstrated by ultrasound as shown in the literature, with a high-resolution linear probe in the evaluation of the joints, concomitantly in the eyeball [22-24].

Modern ocular ultrasound allows a non-invasive examination and dynamic approach to the different intraocular structures, especially when they cannot be observed due to loss of transparency in the optical parts (cornea, lens, and vitreous body) [16]. In our sample, 60 eyes were evaluated; the ocular ultrasound detected a chronic inflammatory process characterized by vitreous echo findings, not detected by the ophthalmological evaluation. An anterior chamber reaction was detected by ophthalmological examination in 9 eyeballs, which were not detected by ultrasound, as they were discrete alterations. In our sample, there was a statistically significant presence of cataract, which can be considered a complication of the uveal chronic inflammatory process detected by ultrasound.

Among the patients who had vitreitis, most were in grade 2 or 3 of echo intensity, that is, greater ocular inflammatory process, a result similar to that already described in the literature [22,24]. In these case reports, the detection of joint alterations characterized by the presence of synovitis and vitritis findings by ultrasound was demonstrated, both in the diagnosis and in the follow-up of the treatment with improvement of the joint and ocular inflammatory process [22,24]. In the literature, the normal vitreous humor is anechoic; the presence of echoes within the vitreous, characterizes hypo and hyperechoic patterns, which may reflect degeneration, inflammation, asteroid hyalosis, hemorrhage and infection in the vitreous [23]. Authors report that with aging, there are changes in the vitreous structure, characterized by liquefaction. The process begins in middle age and, in most cases, progresses slowly into old age. Syneresis is a consequence of changes in the chemical or conformational state of hyaluronic acid and its interaction with collagen [34,35]. Our sample consisted of relatively young patients, with a mean age of 48.1±15.5 years and that showed vitritis by ultrasound; therefore, this findings in our sample are due to the presence of vitreous echoes on ocular ultrasound and not to vitreous syneresis. In addition, the two processes can be well differentiated by the echotextural alteration, and when there are hypo or hyperechoic images floating in the vitreous humor of moderate to significant intensity, then we classify it as vitreitis, which is different when we evaluate the liquid echotexture characterized by an anechoic image [36].

Regarding disease activity indices-ASDAS and BASDAI-in our sample, patients with active disease also had a higher prevalence of vitreitis detected by ultrasound. Some authors evaluated patients with spondyloarthritis who presented with anterior uveitis by clinical ophthalmological examination who had significantly higher BASDAI [37], through a single clinical case, an increase in these indices of joint inflammatory activity and ocular inflammatory changes was observed by ultrasound [24].

Another characteristic evaluated in our study was the thickness of the optic nerve. In our sample, among the patients who exhibited thickening of the optic nerve, 78.3% had vitreitis on ultrasound, with statistical significance. It is suggested that the chronic inflammatory process (vitritis) can thicken the optic nerve as observed by ultrasound. Although ankylosing spondylitis-related uveitis characteristically affects the uveal tract, there are some case reports in the literature that demonstrate optic nerve involvement [38-41].

As limitations of our study, we can mention that the study was a cross-sectional observational, single-center study, and it was not possible to determine causality in our findings. The sample size was small due to the resistance of patients to visit the hospital setting due to the pandemic (data collection carried out from August to September 2021). The sample is heterogeneous. It was not possible to perform the ophthalmological and ultrasound examination in a control group of healthy individuals for comparison purposes.

In conclusion, we observed a significant rate of vitritis on B-mode ultrasonography in patients with spondyloarthritis in axial joint inflammatory activity, as well as evaluating some changes resulting from complications of the chronic uveal inflammatory process, such as cataracts and optic nerve thickening. In the future, ultrasonography with a high-frequency linear probe may be an adjuvant tool in the ophthalmological evaluation of patients with spondyloarthritis.

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