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CLINICAL ASPECTS OF POSTERIOR UVEITIS IN OCULAR SARCOIDOSIS

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SUMMARY – Two clinical forms of the "white spot" syndrome in patients with posterior uveitis in definitive and presumable ocular sarcoidosis were analyzed. Group 1 was characterized by periphlebitis and discrete white spots around the vein of the retina, so-called "candle-wax", whereas group 2 showed yellow-orange solitary nodules located at the choroid, i.e. multifocal choroiditis. Visual acuity and the severity of clinical presentation were assessed in both groups. Visual acuity, Snellen equivalent was 0.52±0.36 in group 1 and 0.82±0.39 in group 2 with lesions at the level of choroid. One-way analysis of variance ANOVA showed a statistically significant between-group difference in visual acuity (p=0.03). The mean severity of clinical presentation was 11.80±2.04 points in group 1 and 5.80±4.18 points in group 2. T-test for independent samples yielded a statistically significant difference between the groups (p=0.02). A statistically significant difference in visual acuity was the result of vasculitis in the group with the "candle-wax" phenomenon, which is associated with retinal vasculitis and causes cystoid macular edema and reduction of visual acuity. Complications such as cataract, glaucoma and neovascularization, which also decrease visual acuity, were more frequent in group 1.

Key words: *Sarcoidosis – etiology; Vasculitis – pathology; "Candle-wax" – pathology; "White dot" – pathology; Multifocal choroiditis – diagnosis; Uveitis – diagnosis*

Introduction

Sarcoidosis is a multisystem idiopathic inflammatory disorder of unknown origin, defined by the presence of non-caseating epithelioid granuloma and accumulation of T lymphocytes[1]. Diagnostic criteria have been proposed based on ocular signs[2], laboratory investigations, and biopsy results[3].

Clinical presentation of ocular sarcoidosis-associated posterior uveitis has been reported by some authors[4] as "*taches de bougie*" or "candle-wax" spots in two clinical forms, each with different visual prognosis[5]. In the first type, these spotted whitish lesions are associated with segmental venous "sheathing", perivenular exudates and vitritis. The second type of posterior uveitis is characterized by yellow-orange lesions located at the level of the choroid, and they are not associated with retinal vasculitis or retinal vascular obliteration[6].

The aim of this study was to observe and describe differences in the prognosis of these two clinical forms of posterior uveitis in our patients with the diagnosis of definitive and probable ocular sarcoidosis, by comparing two parameters, i.e. the best corrected visual acuity and the severity of clinical picture as assessed by complication scoring.

Patients and Methods

This retrospective clinical study was conducted at University Department of Ophthalmology, Clini-

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cal Center in Kragujevac, Serbia, during the 2008-2010 period. The study included 24 patients, mean age 52.1 (range 25-65) years, followed for an average of 3 (range 1-5) years. All patients underwent comprehensive eye examination, which included the best corrected visual acuity (BCVA), slit-lamp biomicroscopy, dilated ophthalmoscopy and fundus photography, fluorescein angiography (FA), optical coherence tomography (OCT) and computerized perimetry.

Using this diagnostic protocol, we were able to identify the following seven ocular signs necessary for the diagnosis of ocular sarcoidosis: 1) mutton-fat keratic precipitates (KPs)/small granulomatous KPs and/or iris nodules (Koeppe/Busacca); 2) trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS); 3) vitreous opacities displaying snowballs/strings of pearls; 4) multiple chorioretinal peripheral lesions (active and/or atrophic); 5) nodular and/or segmental periphlebitis (+/- candle-wax drippings) and/or retinal macroaneurysm in the inflamed eye; 6) optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule; and 7) bilateral involvement[2,6,7].

Upon ruling out other possible causes of uveitis, the diagnosis of definitive ocular sarcoidosis in our patients included biopsy-supported diagnosis with a compatible uveitis[1-7]. Conjunctival biopsy or lacrimal gland biopsy specimens were examined for noncaseating granulomas. Transbronchial (TBB)[8], or transmediastinal (TMB) lymph node biopsy was performed (Table 1).

The diagnosis of presumed ocular sarcoidosis in our patients was based on ocular signs compatible with uveitis[2] and subsequent ancillary investigations including chest radiography[9] to detect bilateral hilar lymphadenopathy (BHL)[2], or computed tomography scan (CT) of the mediastinum in patients with negative chest x-ray results[10], or fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) (Table 1)[3,11].

Laboratory investigations included determination of elevated serum angiotensin converting enzyme (ACE) levels, ionized serum and urine calcium, tuberculin skin test (useful to exclude tuberculosis and anergy to tuberculin antigen), liver enzyme tests and elevated serum lysozyme levels (Table 1)[12,13].

Study patients with presumed and definitive ocular sarcoidosis and clinical presentation of spotted whitish lesions in the posterior segment of the eye were divided into two clinical patterns: group 1 characterized by nodular and/or segmental phlebitis (venous "sheathing" and/or perivenular exudates) and discrete white spots around retinal venules, so-called candle wax drippings; and group 2 characterized by a yellow-orange solitary nodule located at the level of the choroids, multifocal choroiditis and/or optic disc nodule(s)/granuloma(s). Clinical picture of the complications and visual acuity were tested in these two patient groups.

The complication reflects the clinical picture seriousness. The severity of clinical picture in both groups was tested by the following parameters: vitreous body cloudiness, blood vessel layering, macular edema, blood vessel occlusion and neovascularization. In accordance with this, each patient was evaluated from maximum 25 points down to minimum 0 points.

The study included determination of the patient's best corrected visual acuity.

Statistical analysis

Statistical analysis was performed by the SPSS 17.0 software (originally, Statistical Package for Social Sciences) using one-way analysis of variance (ANOVA) and T-test for independent samples. One-way analysis of variance is a statistical test to identify significant differences in the dependent variable based on categorical differences in one independent variable. A significant p-value resulting from one-way ANOVA test would indicate that a gene is differentially expressed in at least one of the groups analyzed. The level of significance was set at $p<0.05$. Kolmogorov-Smirnov test was used to check for the normality of distribution of the complication parameters.

Results

Six (25%) patients with definitive ocular sarcoidosis and 18 (75%) patients with presumed ocular sarcoidosis were observed for an average follow-up period of 3 (range 1-5) years; there were 62.5% of female patients; 70% of patients manifested bilateral disease and 37% of patients had a positive family history. Ocular inflammation preceded any systemic sign of sarcoidosis by more than 1 year in 40% of patients. One patient suffered from thyroid disease, confirming

Table 1. Diagnosis of presumed and definitive ocular sarcoidosis

Patients with presumed ocular sarcoidosis	
Ophthalmic manifestation	
Uveitis anterior:	25%
– mutton-fat KPs/small granulomatous KPs and/or iris nodules (Koeppe/Busacca)	41.6%
– trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)	8.3%
Vitritis snow balls/"string pearls"	14.6%
Uveitis posterior	
Whitish spotted lesions:	
– "candle wax" drippings phenomenon on retinal vessels	25%
– "white dots" of various size	25%
– multifocal choroiditis	
– solitary choroidal nodule	
Vasculitis: - nodular and/or segmental periphlebitis	21%
- retinal macroaneurysm in an inflamed eye	16.6%
Multiple chorioretinal peripheral lesions, active and/or atrophic	35%
Optic neuropathy, nodules/granulomas	/
Bilaterality	70%
Laboratory investigations and investigational procedures	
Elevated serum ACE	87.5%
Elevated serum lysozyme	4.1%
Tuberculin skin test allergy	12.5%
Hilary lymph node enlargement (chest x-ray and/or CT scan)	33.3%
Urine and serum calcium levels	8.3%
Abnormal liver enzyme tests	4.2%
Raised level of serum immunoglobulin	20.8%
Pulmonary function tests – reduced lung capacity	50%
Patients with definitive ocular sarcoidosis	
Transbronchial biopsy	4.2%
Mediastinoscopy biopsy	16.6%
Other localization granulomas biopsy	4.2%

the well-known association between sarcoidosis and autoimmune thyroid disease.

At the time of diagnosis, visual acuity 0.81±0.30 Snellen equivalent was present in patients with presumed ocular sarcoidosis. Patients with definitive ocular sarcoidosis had visual acuity 0.79±0.31 Snellen equivalent. Kolmogorov-Smirnov test showed normal distribution for the parameter of visual acuity. There was no statistically significant between-group difference in visual acuity according to T-test (T test, $p>0.05$).

In our patients, ocular sarcoidosis involved posterior segment in 29.1%, anterior segment in 23.3%, pars planitis in 8.3%, panuveitis in 33% and isolated vitritis in 6.3% of patients. Sarcoidosis-associated posterior uveitis was usually chronic. The most common manifestation of posterior uveitis was retinal vasculitis (37.6%). Phlebitis was found in less than half of the patients with posterior uveitis and may have been associated with candle wax drippings in the middle and distant periphery (Fig. 1). Cellular infiltration of the vitreous may occur in clumps (snowballs), in the inferior vitreous, or in chains (string of pearls).

We found whitish spotted lesions in 50% of patients with sarcoidosis, i.e. associated posterior uveitis.

Table 2. Two clinical patterns in ocular sarcoidosis-associated posterior uveitis

"**Candle wax**" phenomenon on retinal vessels	50%	6
Complications	Σ70 points 11.80	
Visual acuity	0.52±0.36	
"**White dots**" of various size	50%	6
- multifocal choroiditis		
- large choroidal granulomas		
Complications	Σ35 points 5.80	p = 0.02
Visual acuity	0.82±0.39	p = 0.03

Patients were divided into two clinical groups (Table 2): group 1 with "white dots" phenomenon, characterized by vitritis with segmental venous "sheathing" or perivenular exudates and discrete white spots around retinal venules, "candle-wax" (40%). Small, discrete white spots occur in clusters around retinal venules, often limited to the inferior quadrant; and group 2 with "white dots" phenomenon characterized by yellow-orange lesions located at the level of the choroid, predominantly in the posterior and nasal fundus simulating the lesion of birdshot chorioretinopathy. These are discrete and depigmented lesions, but some of them were atrophic. They are not associated with retinal vasculitis or retinal vascular obstruction. These granulomas may take the form of multifocal choroiditis or large choroidal granulomas.

The severity of the clinical picture and visual acuity were tested in both groups.

In group 1, cataract as a complication was recorded in 75% and cystoid macular edema in 50% of patients. Peripheral capillary closure was a feature of sarcoidosis in 25% of patients. Hemophthalmos was seen in 16.6% and exudative retinal detachment in 8.3% of patients. In the study group, the clinical picture severity was 11.80±2.04 points and visual acuity Snellen equivalent 0.52±0.36. Visual prognosis was better in patients with the latter type.

Visual acuity was better in group 2 with lesions at the level of the choroids (0.82±0.39 Snellen equivalent). One-way analysis of variance ANOVA yielded a statistically significant between-group difference in visual acuity (p=0.03). In group 2, macular edema was noted clinically and/or angiographically and by optical coherence tomography in only 8.3%. Cataract and glaucoma were also observed in 8.3% of patients in this group. In this group of patients, the mean

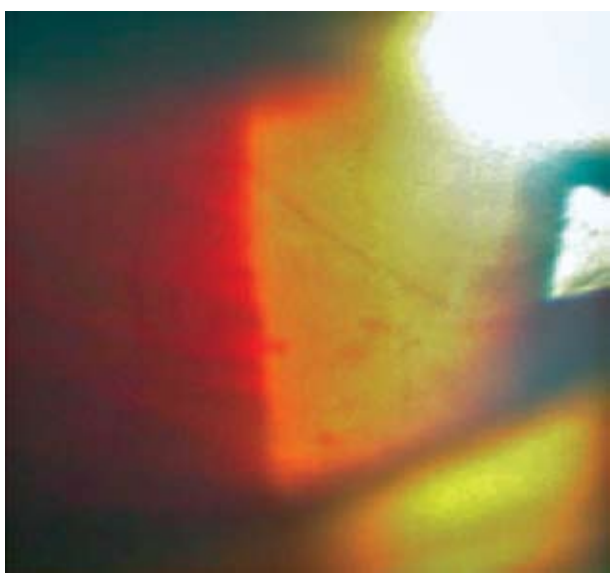

Fig. 1. Phlebitis with "candle-wax drippings" and "snow bank" in a 65-year-old woman with ocular sarcoidosis (photo fundus).

score indicating the severity of clinical picture was 5.80±4.18 points. Kolmogorov-Smirnov test showed normal distribution for the complication parameters. T-test for independent samples yielded a statistically significant difference between the groups (p=0.02).

Discussion

Good visual acuity was present in most patients with presumed ocular sarcoidosis and there were no extensive areas of exudation[14,15]. Patients with definitive ocular sarcoidosis and compatible uveitis had somewhat worse visual acuity and somewhat poorer prognosis[16]. There was no statistically significant difference in visual acuity between these two groups of patients.

We found whitish spotted lesions in 50% of patients with ocular sarcoidosis. The first type of whitish spotted phenomenon, named "candle-wax", was associated with retinal vasculitis and vitritis and had a statistically significantly worse visual acuity than the other group of patients. Visual acuity is worse due to retinal inflammation. Retinal inflammation and vasculitis result in cystoid macular edema[17].

Retinal vasculitis is a major sign of posterior segment involvement in ocular sarcoidosis, although not pathognomonic and predominantly involving the veins. Vasculitis is often located at the end of periphery, between the equator and the ora serrata, and also juxtamacular region in the vast majority of patients with ocular sarcoidosis[18]. Peripheral capillary closure is a feature of sarcoidosis, but also of tuberculosis, Eales disease, and in rare instances multiple sclerosis, Behçet's syndrome, and slow-flow retinopathy may have a similar picture[19]. The ability to identify retinal vasculitis and the presence or absence of retinal ischemia by fluorescein angiography has important implications for management in this situation. In the former case, laser photocoagulation may be indicated, although there is a risk of exacerbating macular edema, whereas in the latter, appropriate immunosuppression will usually induce regression of neovascular response.

The second type of whitish spotted lesions located at the level of the choroid simulates the "white dots" syndrome. Exacerbation of this type of granulomatous uveitis is often associated with the appearance of iris or retinal nodules[20]. Pharmacological control of this type of uveitis is followed by complete disappearance of granulomas. Visual prognosis was related to the course of uveitis, but was better in patients exhibiting the second type, with lesions located at the level of the choroid.

We found that visual acuity and severity of complications differed significantly according to the level of localization of inflammation in the retina and choroid. On the other hand, there was no significant difference in visual acuity between histologically confirmed ocular sarcoidosis and presumed ocular sarcoidosis.

In bilateral chronic uveitis and posterior uveitis, systemic corticosteroid therapy is always the first-line approach (42%). Systemic corticosteroids produce undeniably quick anti-inflammatory effect, particularly in the acute phase. It is essential to initiate therapy with high daily doses of methylprednisolone, in morning doses for at least 5-7 days, then tapering it gradually to the maintaining dose (15-30 mg/day). However, in patients that poorly tolerate and are refractory to corticosteroids[21], methotrexate has been shown to be most potential as alternative treatment (16.6%). Methotrexate has a delayed onset of action, requiring 3 to 6 weeks to take effect and has been used in conjunction with steroids to control inflammation. We initiate methotrexate therapy with a weekly dose of 2.5 mg to 10 mg administered orally or intramuscularly, as either a single dose or divided doses over a 36- to 48-hour period. The dose is gradually increased as dictated by the clinical response to a maximum of 50 mg/week[22].

Conclusion

Posterior uveitis accompanied by white dotted changes is classified into two clinical forms that are statistically significantly different in visual acuity and the severity of clinical picture, i.e. complications. Statistically significant differences in visual acuity between these two groups are the result of vasculitis in the group with "candle-wax" phenomenon that is associated with vasculitis of the retina and is causing cystoid macular edema and a decrease in visual acuity. Complications such as cataract, glaucoma and neovascularization that also decrease visual acuity were more common in this group.

References

1. FOSTER S, VITALE A. Diagnosis and treatment of uveitis. In: PANAGIOTA S, FOSTER S, editors. Sarcoidosis. Philadelphia: W.B. Saunders, 2002:710-25.
2. HERBOT CP, RAO NA, MOCHIZUKI M. International criteria for diagnosis of ocular sarcoidosis: results of the first International Workshop on Ocular Sarcoidosis (IWOC). Ocul Immunol Inflamm 2009;17(3):160-9.
3. CLEMENT DS, POSTMA G, ROTHOVA A, GRUTTERS JC, PROKOP M, De JONG PA. Intraocular sarcoidosis: association of clinical characteristics of uveitis with positive chest high-resolution computed tomography findings. Br J Ophthalmol 2010;94(2):219-22.
4. EDELSTEN C, STANFORD MR, GRAHAM EM. Serpiginous choroiditis: an unusual presentation of ocular sarcoidosis. Br J Ophthalmol 1994;78:70-1.
5. VRABEC T, AUGSBURGER J, FISCHER D, BELMONT J. Taches de bougie. Ophthalmology 1995;102:1712-21.
6. ABAD S, MEYESSONIER V, ALLALI J, GOUYA H, GIRAUDET AL, MONET D. Association of peripheral multifocal choroiditis with sarcoidosis: a study of thirty-seven patients. Arthritis Care Res 2004;51(6):974-82.
7. ROTHOVA A. Ocular involvement in sarcoidosis. Br J Ophthalmol 2000;84:110-6.
8. GERASIN VA, MOLODSTOVA VP, DVORAKOVSKIA IV, DEREVIANKO AV, BAZHANOV AA, BARANOVA OO. Transbronchial biopsy of the lungs in diagnosis of respiratory sarcoidosis. Ter Arkh 2008;80(4):43-6.
9. IVIČEVIĆ, A, PEROŠ-GOLUBIČIĆ, T, HUIĆ, D, TEŽAK, S, GOREČAN, M, TEKAVEC-TRKANJEC, J, ALILOVIĆ, M. Correlation of lung gallium-67 scintigraphy with lung x-ray and pulmonary function tests in patients with sarcoidosis. Act Clin Croat 2003;42:91-9.
10. KIYOTAKE R, OKINAMI S, SOMA M, HIRATA A, ISHIGOOKA H, KITA M, INADA K. Evaluation of revised diagnosis criteria for sarcoidosis. Nippon Ganka Gakkai Zasshi 2010;114(8):678-82.
11. TAKAHASHI T, AZUMA A, ABE S, KAWANAMI O, OHARA K, KUDOH S. Significance of lymphocytosis in bronchoalveolar lavage in suspected ocular sarcoidosis. Eur Respir J 2001;18(3):515-21.
12. JOVANOVIĆ S, VUKOSAVLJEVIĆ M, JOVANOVIĆ M, STANOJEVIĆ-PAOVIĆ A. Oftalmološke manifestacije hronične sarkoidoze. Ser J Exp Clin Res 2008;9(1):27-30.
13. TAKEUCHI M, OH I K, SUZUKI J, HATTORI T, TAKEUCHI A, OKONUKI Y, *et al*. Elevated serum levels of CXCL9/monokine induced by interferon-γ and CXCL10/interferon-γ-inducible protein-10 in ocular sarcoidosis. Invest Ophthalmol Vis Sci 2006;47(3):1063-8.
14. LAUBY TJ. Presumed ocular sarcoidosis. Optometry 2004;75(5):297-304.
15. MEZAINE HS, Al-MUAMMAR A, KANGAVE D, ABU El-ASRAR AM. Clinical and optical coherence tomographic findings and outcome of treatment in patients with presumed tuberculous uveitis. 2008;28(6):413-23.
16. LOBO A, BARTON K, MINASSIAN D, Du BOIS RM, LIGHTMAN S. Visual loss in sarcoid-related uveitis. Clin Exp Ophthalmol 2003;31(4):310-6.
17. MISEROCCHI E, MODORATI G, Di MATTEO F, GALLI L, RAMA P, BANDELLO F. Visual outcome in ocular sarcoidosis: retrospective evaluation of risk factors. Eur J Ophthalmol 2011;21(6):802-10.
18. OHARA K, JUDSON MA, BAUGHMAN RP. Clinical aspects of ocular sarcoidosis. Eur Respir Mon 2005;32:188-209.
19. ABU El-ASRAR AM, HERBORT CP, TABBARA KF. Differential diagnosis of retinal vasculitis. Middle East Afr J Ophthalmol 2009;16(4):202-18.
20. FORSTER DJ. General approach to the uveitis patient and treatment strategies. In: Yanoff M, Duker JS, editors. Ophthalmology. Philadelphia: Mosby, 2009:783-8.
21. PRANIĆ-KRAGIĆ A, RADIĆ M, RADIĆ I. Glucocorticoid induced osteoporosis Acta Clin Croat 2011;50(4):563-6.
22. ZLATANOVIĆ G, JOVANOVIĆ S, ŽIVKOVIĆ M, ZLATANOVIĆ M, SREĆKOVIĆ S, RADOTIĆ F. The efficacy of novel therapeutic modalities of isolated ocular vasculitis *vs* ocular vasculitis as a systemic disease. Med Glas Ljek komore Zenicko-Doboj kantona 2012;9(1):66-73.

Sažetak

KLINIČKI ASPEKTI STRAŽNJEG UVEITISA KOD OČNE SARKOIDOZE

S. V. Jovanović, Z. D. Jovanović, F. M. Radotić, S. B. Srećković, S. S. Paunović i *J. D. Stojanović*

Analizirana su dva klinička oblika sindroma "bijelih točaka" kod bolesnika sa stražnjim uveitisom u okviru definitivne i pretpostavljane sarkoidoze oka. Prva skupina je imala periflebitis i diskretne bijele mrlje oko venula mrežnice, tzv. "kapi svijeće". Druga skupina je imala žuto-narančaste solitarne čvoriće na razini koroida, tj. multifokalni koroiditis. Ispitana je vidna oštrina i težina kliničke slike obiju skupina. Vidna oštrina, Snellenov ekvivalent bio je 0,52±0,36 u prvoj skupini i 0.82±0,39 u drugoj skupini s lezijama na razini koroida. Jednosmjerna analiza varijance ANOVA je pokazala statistički značajnu razliku u vidnoj oštrini (p=0,03). Težina kliničke slike bila je 11,80±2,04 bodova za prvu skupinu i 5,80±4,18 bodova za drugu skupinu. T-testom za nezavisne uzorke izračunata je statistički značajna razlika između skupina (p=0,02). Statistički značajna razlika u vidnoj oštrini bila je rezultat vaskulitisa u skupini s fenomenom "kapi svijeće" koji je povezan s vaskulitisom mrežnice te uzrokuje cistoidni edem makule i smanjenje vidne oštrine. Komplikacije kao što su katarakta, glaukom i neovaskularizacija koje također utiču na smanjenje vidne oštrine bili su češći u prvoj skupini.

Ključne riječi: *Sarkoidoza – etiologija; Vaskulitis – patologija; "Kapi svijeće" – patologija; Sindrom "bijelih točaka" – patologija; Multifokalni koroiditis – dijagnoza; Uveitis – dijagnoza*