EXTENDED REPORT

Vitreoretinal morphology in active ocular toxoplasmosis: a prospective study by optical coherence tomography

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Aim: To investigate the third generation optical coherence tomography (OCT3) findings in patients with active ocular toxoplasmosis.

Methods: A prospective observational case series, including 15 patients with active ocular toxoplasmosis in at least one eye evaluated at a single centre. Vitreoretinal morphological features at baseline and changes within a 24-week follow-up interval on OCT3 were evaluated.

Results: The active ocular toxoplasmosis lesion was classified clinically as punctate (n=6), focal (n=6) or satellite (n=3). Retinal layers were hyper-reflective at the active lesion site, and some degree of retinal pigment epithelium-choriocapillaris/choroidal optical shadowing was seen in all patients. In general, the retina was thinned at the active lesion site in eyes with punctate lesions and thickened in eyes with focal and satellite lesions. When detected by OCT3, the posterior hyaloid appeared thickened. While focally detached over punctate lesions, the posterior hyaloid was partially detached, but still attached to the lesion in focal and satellite lesions. Additional findings (not detected on clinical examination) include diffuse macular oedema (n=6), vitreomacular traction (n=3) and maculoschisis (n=1). During follow-up, a decrease in retinal thickness and focal choriocapillaris/choroidal relative hyper-reflectivity were observed at the former lesion site, and posterior vitreous detachment progressed/occurred in all patients.

Conclusion: OCT3 enabled identification of morphological features underestimated on clinical examination in patients with ocular toxoplasmosis, which may expand the clinical spectrum of the disease. Further studies are needed to verify the relevance of OCT3 in assisting with the diagnosis and management of ocular toxoplasmosis.

Toxoplasma gondii infection has worldwide distribution, and toxoplasmic retinochoroiditis is the most common form of posterior uveitis in otherwise healthy individuals.¹ The prevalence of seroconversion varies in different regions, depending on socioeconomic, geographic and climatic factors. For example, the prevalence of seropositivity in Brazil ranges from 50% to 83%,^{2,3} and that in the US from 30% to 70%.⁴ Classically, toxoplasmic retinochoroiditis appears as a focus of inner retinitis adjacent to an old chorioretinal scar, and is accompanied by vitritis. During the healing process, the acute lesions resolve, leaving a chorioretinal scar with well-defined hyperpigmented borders and central chorioretinal atrophy. However, considerable variation in the clinical features of disease,^{5–13} including punctate outer retinal toxoplasmosis,^{14,15} raises the question whether or not atypical cases may represent different forms of the disease. The differentiation between congenital and postnatally acquired infections, which is relevant from the point of view of counselling and of screening programmes for children, has also been considered, to date, a difficult task in many instances.^{6,16–18}

Additional clinical insights into the disease may have important implications for the understanding of tissue damage mechanisms, with implications for the management and prognosis, as well as help future research efforts. The current study investigates third generation optical coherence tomography (OCT3) findings during acute disease and over a 24-week period of follow-up in patients with various clinical forms of active ocular toxoplasmosis.

PATIENTS AND METHODS

A prospective observational case series including patients with biomicroscopic evidence of active ocular toxoplasmosis was

designed to evaluate the OCT3 findings during acute disease and their changes over a 24-week period of follow-up. The study protocol was approved by the institutional review board of the Federal University of Minas Gerais, and all participants gave written informed consent. All patients underwent fundus photography and OCT3 evaluation by the same experienced certified ophthalmic technician under the supervision of one of the authors (JLO). Data evaluation was performed by uveitis and retinal specialists (JLO and RAC).

All patients evaluated at the Uveitis Section of the Department of Ophthalmology, Federal University of Minas Gerais, with a diagnosis of active ocular toxoplasmosis between July 2004 and June 2006 were invited to participate in the study. The diagnosis was based on the criteria described by Holland and colleagues⁵: the presence of an active white focal retinal lesion, with or without associated hyperpigmented chorioretinal scars, and confirmed by laboratory studies. All patients were treated with sulphadiazine 500 mg orally four times a day, pyrimethamine 25 mg orally twice daily and folinic acid 5 mg three times a week, as well as prednisolone (0.5 mg/kg) orally once daily.

At baseline, each patient received a detailed ophthalmological examination including best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, slit lamp biomicroscopy, dilated biomicroscopic and fundus examinations, and colour fundus photography. OCT3 evaluation (Stratus Tomographer, Model 3000, Carl Zeiss Ophthalmic Systems, Humphrey Division, Dublin, California, USA) was

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; OCT3, third generation optical coherence tomography; RPE, retinal pigment epithelium

Figure 1 Colour fundus photography at baseline and optical coherence tomography (OCT) evaluations at baseline and at 12 (2) weeks of two patients with ocular toxoplasmosis. (A, punctate lesion) At baseline, retinal pigment epithelium-choriocapillaris/choroidal optical shadowing was observed at the active lesion site (asterisk). Note that the posterior hyaloid was thickened and detached (arrowheads) over the lesion and contained irregular hyper-reflective formations (arrow). Subsequent evaluation at week 12 demonstrated extended detachment of the posterior hyaloid and the presence of a persistent hyper-reflective structure at the level of the retinal surface (open arrowheads), which may indicate the occurrence of vitreoschisis. (B, focal lesion) Note that despite classification on clinical examination as a focal lesion, similar findings on OCT evaluation were seen.

Figure 2 Colour fundus photography and third generation optical coherence tomography evaluations at baseline in two patients with active ocular toxoplasmosis. (A, focal lesion) Posterior hyaloid was thickened and partially detached (from the optic disc to the temporal aspect of the posterior pole (arrowheads)) with complete vitreofoveal separation. At the lesion site, note the increase in retinal thickness and increased reflectivity from the inner retinal layer, with subadjacent optical shadowing (asterisk); posterior hyaloid was thickened and attached to the active lesion. (B, satellite lesion) At baseline, subretinal fluid (arrows) was observed next to the active lesion (asterisk).

Table 1 Baseline clinical characteristics and follow-up evaluation

Patient no, age (years), sex, race	Study eye	Serum IgG/IgM*	Lesion Type	Location	Size	Baseline evaluation		Follow-up evaluation	
						BCVA (logMAR)	Clinical findings†	BCVA (logMAR)	Clinical findings†
1, 20, F, W	OD	+/-	Punctate	Zone 1	<1 DD	20/63 (0.5)	ACC = 2+; ACF = 1+; VC = present	20/20 (0.0)	Inactive; hypopigmented scar
2, 33, M, W	OD	+/-	Punctate	Zone 1	<1 DD	20/40 (0.3)	ACC = 1+; ACF = 1+; VC = present; local vasculitis	20/20 (0.0)	Inactive; FEF; hypopigmented scar
3, 27, M, W	OS	+/-	Punctate	Zone 2	<1 DD	20/100 ⁻¹ (0.68)	ACC = 0.5+; ACF = 1+; VC = present; FEF; old scar; retinal tear	20/40 ⁻² (0.34)	Inactive; FEF; hypopigmented scar
4, 51, M, W	OS	+/-	Punctate	Zone 1	<1 DD	20/32 (0.2)	ACC = 1+; ACF = 1+; VC = present; old scars	20/25 (0.08)	Inactive; hypopigmented scar
5, 16, F, W	OS	+/-	Punctate	Zone 2	<1 DD	20/40 (0.3)	ACC = 2+; ACF = 1+; VC = present; old scar	20/20 (0.0)	Inactive; hypopigmented scar
6, 18, F, W	OD	+/-	Punctate	Zone 1	<1 DD	20/80 (0.6)	ACC = 2+; ACF = 1+; VC = present; old scars	20/63 (0.5)	Inactive; hypopigmented scar
7, 12, M, W	OS	+/-	Focal	Zone 1	<1 DD	20/200 ⁻¹ (1.02)	ACC = 1+; ACF = 1+; VC = present; local vasculitis	20/20 ⁻² (0.04)	Inactive; hypopigmented scar
8, 23, M, W	OD	+/+	Focal	Zone 2	1-2 DD	20/50 ⁻² (0.44)	ACC = 2+; ACF = 1+; VC = present; local vasculitis	20/20 (0.0)	Inactive; hyperpigmented scar
9, 21, M, W	OD	+/-	Focal	Zone 1	1-2 DD	20/40 (0.3)	ACC = 1+; ACF = 1+; VC = present; EM; incomplete PVD	20/25 (0.1)	Inactive; hyperpigmented scar
10, 22, M, W	OD	+/-	Focal	Zone 1	1-2 DD	20/400 (1.3)	ACC = 3+; ACF = 2+; VC = present; IRH; local vasculitis	20/63 ² (0.46)	Inactive; hyperpigmented scar
11, 49, M, W	OS	+/+	Focal	Zone 1	<1 DD	20/80 (0.6)	ACC = 1+; ACF = 0; VC = present; granulomatous KP	20/25 (0.08)	Inactive; hyperpigmented scar
12, 14, M, W	OS	+/-	Focal	Zone 1	1-2 DD	20/50 ⁻² (0.44)	ACC = 2+; ACF = 1+; VC = present	20/20 ⁻¹ (0.02)	Inactive; hyperpigmented scar
13, 26, M, W	OS	+/-	Satellite	Zone 1	<1 DD	20/80 (0.6)	ACC = 1+; VC = present; granulomatous KP; EM; old scars	20/25 (0.08)	Inactive; hyperpigmented scar
14, 25, F, W	OS	+/-	Satellite	Zone 2	1-2 DD	20/50 ⁻² (0.44)	ACC = 2+; ACF = 1+; VC = present; old scar	20/25 ² (0.06)	Inactive; hyperpigmented scar
15, 28, M, W	OD	+/-	Satellite	Zone 2	<1 DD	20/40 (0.3)	ACC = 3+; ACF = 2+; VC = present; old scar; generalised vasculitis	20/20 (0.0)	Inactive; residual vasculitis; hyperpigmented scar

ACC, anterior chamber cells; ACF, anterior chamber flare; BCVA, best-corrected visual acuity; DD, disc diameter (1.5 mm); EM, exudative maculopathy; ETDBS, Early Treatment Diabetic Retinopathy Study; F, female; FEF, focal epiretinal formation; IRH, intraretinal haemorrhage; IU, international unit; KP, keratic precipitates; M, male; OD, right eye; OS, left eye; PVD, posterior vitreous detachment; VC, vitreous cells; W, white.

*IgG (positive > 8 IU/ml); IgM (positive > 6.5 IU/ml).

†According to the Standardization of Uveitis Nomenclature working group.

Table 2 Optical coherence tomography findings at baseline and changes during follow-up

OCT findings	Lesion type			Total (n = 15)
	Punctate (n = 6)	Focal (n = 6)	Satellite (n = 3)	
Baseline				
Posterior hyaloid				
Thickened, focally detached (over the focus)	6	1	0	7
Thickened, fully detached	–	1	–	1
Thickened, attached to the focus and detached around it	–	4	1	5
“Hairy” appearance	1	1	1	3
Containing irregular hyper-reflective formations	4	–	–	4
Lesion				
Increased reflectivity from inner retinal layers	6	6	3	15
Some RPE-cc/Ch optical shadowing	6	6	3	15
Decreased retinal thickness	4	1	–	5
Apparently normal retinal thickness	2	–	1	3
Increased retinal thickness	–	5	2	7
Subretinal fluid adjacent to the focus	–	–	2	2
Macula				
No noticeable changes	2	2	–	4
Inner surface increased reflectivity	3	4	–	7
Inner surface contour irregularities	3	4	–	7
Diffuse intraretinal oedema	1	3	2	6
Tractional maculopathy*	2	–	1	3
Disorganised signalling from old macular scar	1	–	–	1
Follow-up				
Posterior hyaloid				
Expanded detachment	6	3	1	10
Thickened, adherent to the focus and detached around it†	–	–	2	2
Epiretinal hyper-reflective formation	5	5	1	11
Containing irregular hyper-reflective formations†	1	1	–	2
Lesion				
Decreased retinal thickness	6	6	3	15
Focal RPE-cc/Ch relative hyper-reflectivity	6	6	3	15
Disorganised reflectivity from retinal layers	6	6	3	15
Resolved subretinal fluid	–	–	2	2
Fibrotic proliferation (“mound”)	–	2	–	2
Macula				
Inner surface increased reflectivity†	1	–	1	2
Inner surface contour irregularities†	–	1	1	2
Resolved retinal oedema	1	3	2	6
Residual tractional maculopathy	1	–	–	1
Complete relieve of tractional maculopathy	1	–	1	2

OCT, optical coherence tomography; RPE-cc/Ch, retinal pigment epithelium-choriocapillaris/choroidal.

*With or without vitreofoveal traction.

†Not identified at presentation.

performed in all patients, and consisted of six linear scans oriented at 30° intervals and centred on the foveal region, as well as several scans of the fundus area encompassing the toxoplasmic lesion, which were oriented at the discretion of the supervising uveitis specialist (JLO). These latter scans were recorded so as to ensure use of a similar scanning protocol at subsequent visits. Scans 6 mm in length were used to optimise identification of retinal structures; scans 8 and 10 mm in length were used to evaluate the vitreoretinal interface.

All patients were scheduled for a follow-up visit at 12 (2) weeks and/or 24 (2) weeks after baseline evaluation. At these follow-up visits, patients underwent a comprehensive ophthalmic examination using the same procedures as at baseline. Clinical data were analysed by uveitis and retinal specialists (JLO and RAC) in conformity with the Standardization of Uveitis Nomenclature working group.¹⁹ Additional visits were performed as judged necessary by the treating doctors.

RESULTS

During the study period, active ocular toxoplasmosis was identified in 61 patients on the basis of clinical examination and laboratory studies. In all, 18 patients refused to participate,

and in 28 patients anterior or posterior chamber opacities prevented acquisition of adequate posterior segment photography and OCT images. The remaining 15 patients were included in the study.

All 15 patients who were enrolled completed at least one follow-up visit. The mean (SD) age of the 11 (73.3%) men and 4 (26.7%) women was 25.7 (11.3) years (median, 23 years; range, 12–51 years). Anti-toxoplasma antibody analysis revealed positive IgG titres in all patients. IgM titres were positive in two patients (patients 8 and 11). Best-corrected ETDRS visual acuity (logarithm of the minimum angle of resolution values) ranged from 20/32 (0.2) to 20/400 (1.3) (median, 20/50^{−2} (0.44); mean (SD), 0.53 (0.29)) on presentation. The size of the active toxoplasmic lesion was 1 disc diameter or less in 66.6% (10/15) of patients and was located posteriorly in 66.6% (10/15) different sets of patients. Lesions were classified on the basis of the clinical appearance, as “punctate” in 6 (40%) patients, “focal” in 6 (40%) and as “satellite” in the remaining 3 (20%) patients (table 1).

OCT3 demonstrated that, in patients with punctate lesions, the posterior hyaloid was thickened and focally detached (over the lesion) in all six patients, and contained irregular hyper-reflective formations in four patients at baseline. At the lesion

Figure 3 Colour fundus photography and third generation optical coherence tomography evaluations in one patient with active ocular toxoplasmosis (satellite lesion). (A) At baseline, increased reflectivity from inner retinal layers with subjacent optical shadowing (asterisk) was observed at the active lesion site. Macular oedema detected on clinical evaluation turned out to be maculoschisis. No signals from the posterior hyaloid were detected. (B, C) Subsequent evaluations at weeks 2 and 10 demonstrated a partially detached posterior hyaloid next to the lesion (arrowheads), resolution of the maculoschisis and choriocapillaris/choroidal relative hyper-reflectivity (asterisk) at the former lesion site.

site, the inner retinal layers were abnormally hyper-reflective and some degree of retinal pigment epithelium (RPE)-choriocapillaris/choroidal optical shadowing was observed in all six patients. The retina was clearly thinned at the lesion site in four of the six patients. Contour irregularities and somewhat increased reflectivity of the inner retinal surface of the macula were observed in three eyes. Two eyes presented with vitreomacular traction due to incomplete vitreofoveal separation. During follow-up, the following changes were identified in all patients: (a) expanded separation of the posterior hyaloid; (b) decreased retinal thickness at the lesion site; and (c) disorganised retinal signalling at the lesion site associated with subjacent choriocapillaris/choroidal relative hyper-reflectivity (fig 1A). In the two eyes which presented with vitreofoveal traction, complete vitreofoveal separation was observed in one (patient 3), and partial relief of traction in the other (patient 1).

In the six eyes which presented with a focal lesion at baseline, a different scenario was revealed by serial OCT3 evaluations. At the lesion site, the neurosensory retina was elevated in all but one patient, and the posterior hyaloid was markedly thickened and detached, but adherent to the lesion in 66.6% (4/6) of the patients. Complete vitreofoveal separation was already observed at baseline in five patients (fig 2A). In all, three (50%) patients presented with macular oedema due to diffuse intraretinal fluid. During follow-up, the retina was thinned at the lesion site, and subjacent choriocapillaris/choroidal relative hyper-reflectivity was evident in all patients. Epiretinal hyper-reflectivity was identified in close proximity to the original toxoplasmic focus in five patients, with two patients demonstrating an epiretinal hyper-reflective "mound". Macular oedema observed at baseline was resolved in all three patients (table 2).

The remaining three patients presented with active satellite lesion. OCT features in such eyes included increased retinal thickness at the lesion associated with adjacent subretinal fluid

and diffuse macular oedema in two patients (fig 2B). In one, maculoschisis associated with subretinal fluid was also observed (fig 3A). A thickened posterior hyaloid adherent to the lesion and to the macular centre was seen in the other patient. During follow-up, the subretinal fluid and macular oedema/elevation resolved, and signals corresponding to a thickened posterior hyaloid could be identified adherent to the lesion and separated from the retina close to the lesion in the two patients in whom no signals from the posterior hyaloid were initially seen. In patient 15, complete vitreofoveal separation occurred and an epiretinal hyper-reflective formation was observed (table 2).

At the last follow-up visit, best-corrected ETDRS visual acuity (logarithm of the minimum angle of resolution values) ranged from 20/20 (0.0) to 20/63 (0.5) (median, 20/25² (0.06); mean (SD), 0.12 (0.17)). All six patients with punctate retinochoroiditis had hypopigmented scars, and in two of these patients focal epiretinal formation was observed. In contrast, all except one patient with focal and satellite retinochoroiditis had hyperpigmented scars, and persistent vasculitis was observed in one patient with satellite lesions (patient 15).

DISCUSSION

We evaluated the morphological features of the posterior pole in selected patients with active ocular toxoplasmosis who were followed for 24 weeks. The current study indicates that OCT enables identification of subtle morphological features not detectable on clinical examination, which expand the clinical spectrum of this disease. Macular involvement, such as oedema for example, which has been reported to be an uncommon finding associated with ocular toxoplasmosis for unknown reasons,^{20, 21} was observed in only two of the 15 patients by clinical evaluation; however, OCT demonstrated that the macula was diffusely thickened because of intraretinal fluid in 40% (6/15) of the patients. In addition, three other patients

Figure 4 Colour fundus photography and third generation optical coherence tomography evaluations in one patient with active ocular toxoplasmosis (satellite lesion). The posterior hyaloid, which was not detected on presentation, became thickened with progressive detachment during follow-up (arrowheads).

presented with vitreomacular traction associated with changes of the vitreoretinal interface, including vitreofoveal traction in one patient. Macular elevation observed clinically in one patient and classified as exudative maculopathy (ie, oedema) was demonstrated on OCT to be maculoschisis associated with subretinal fluid (fig 3). It was also noteworthy that, in two of the three eyes with satellite lesions (ie, active retinochoroiditis focus at the margin of an old scar), the posterior hyaloid was not detected on presentation but became thickened and partially detached during follow-up (figs 3 and 4). The fact that the posterior hyaloid was apparently normal and attached on presentation, even in the presence of an old scar, is interesting. Whether or not such findings suggest that the presence of old scar with no obvious changes at the level of the vitreoretinal interface corresponds to congenital lesions remains to be determined in future research.

In its typical presentation of a solitary focus of active retinochoroiditis adjacent to a chorioretinal scar, the diagnosis is generally made promptly. However, diagnosis of ocular toxoplasmosis in immunocompromised patients as well as in immunocompetent patients with atypical presentations of the disease may lead to a delay in diagnosis and management, which may result in a worse outcome due to delayed institution

of anti-toxoplasma therapy.^{12–22} The evaluation of OCT may play a role in assisting the diagnosis of atypical forms of presentation of ocular toxoplasmosis, particularly when presenting as punctate lesions.²³ Although further studies are still required to confirm our initial observations, the identification on OCT of a thickened posterior hyaloid containing irregular hyper-reflective formations and focally detached over a subjacent area of abnormally thinned and hyper-reflective retina, to date, is highly suggestive of an active lesion in ocular toxoplasmosis.

The medical management of ocular toxoplasmosis is still controversial. Should we treat all patients with active ocular toxoplasmosis? If so, until when or for how long should we maintain specific treatment? On the basis of lesion activity, are there reliable clinical features, which indicate that a lesion has indeed healed? Objective data could help in answering some of these questions. The results of the current study suggest that, among the three different active ocular toxoplasmosis lesions (punctate, focal and satellite) studied, common morphological features may be demonstrated on OCT. Increased retinal reflectivity and RPE-choriocapillaris/choroidal optical shadowing at the active lesion site were observed in all 15 patients at baseline. All lesions were considered healed by clinical examination during study follow-up, and the following changes

Figure 5 Colour fundus photography and third generation optical coherence tomography evaluations in one patient with active ocular toxoplasmosis (focal lesion). At baseline, increased reflectivity from the inner retinal layers with superjacent “hairy” appearance of the detached posterior hyaloid and subjacent optical shadowing (asterisk) was observed at the active lesion site. At weeks 2 and 6, some degree of choriocapillaris/choroidal optical shadowing was still evident. By 11 weeks, however, OCT revealed change in the reflective pattern at the former lesion site, with choriocapillaris/choroidal relative hyper-reflectivity (asterisk).

at the original lesion site were demonstrated on OCT: disorganised retinal signalling and decreased retinal thickness, as well as focal choriocapillaris/choroidal relative hyper-reflectivity. Taken together, these findings may serve as an indicator of disease activity and, if so, may assist with management of the disease (eg, whether or not to treat, tapering schedule of corticosteroids, and timing of discontinuation of sulphadiazine and pyrimethamine treatment) (fig 5).

Concepts about ocular toxoplasmosis are evolving,^{16 21 24–27} and its management remains controversial even among uveitis specialists,²⁸ thus indicating a need for additional studies enabling better understanding of the pathophysiology of ocular toxoplasmosis and for the development of better treatment strategies. The current study has several limitations, including a small sample size and potential selection bias, and, therefore, definitive conclusions cannot be made at this time. However, our findings suggest that OCT may enable identification of subtle morphological features not detectable on clinical examination in patients with ocular toxoplasmosis, thus providing new insights about the understanding of the disease, which may assist with the diagnosis and management of the most frequent cause of posterior uveitis affecting both children and adults worldwide.²⁹

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