TITLE:

Ocular toxoplasmosis: phenotype differences between Toxoplasma IgM positive and IgM negative patients in a large cohort.

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SYNOPSIS

Retrospective study to examine the differences in the clinical characteristics and demographics of patients diagnosed of ocular toxoplasmosis according to theirs IgM status. IgM positive were more likely to have macular involvement.

ABSTRACT

Purpose: To investigate the differences in demographics and clinical characteristics of patients diagnosed with ocular toxoplasmosis according to their IgM status.

Methods: Retrospective case note analysis was carried out on patients who tested positive for serum *T.gondii*-specific IgM antibodies (IgM+) as well as a comparator group who tested negative for serum IgM (IgM-), but positive for serum IgG. Patient demographics and clinical features were compared between the two groups to evaluate for any significant differences.

Results: One hundred and six patients were included in the study between March 2011 and June 2018, consisting of 37 in the IgM+ group and 69 in the IgM- group. Patients in the IgM+ group were significantly older (51.1 vs 34.1 years, $p<0.0001$), more likely to present with central macular lesions (32% vs 12%, $p=0.012$), and more likely to develop rhegmatogenous retinal detachment (11% vs 1%, $p=0.049$). In contrast, patients in the IgM- group were more likely present with pain (20% vs 3%, 0.017) and exhibit more severe inflammation of the anterior chamber and vitreous ($p<0.05$). Overall, retinal lesions were more likely to be superotemporal (55%) and superonasal (31%). Furthermore, age was associated with larger ($p=0.003$), and more peripheral lesions ($p=0.007$).

Conclusions: This study demonstrated significant differences in clinical characteristics of ocular toxoplasmosis according to serum IgM status. IgM+ patients were older, less likely to report pain, had lower levels of intraocular inflammation, but were more likely to have macular involvement. We also found age to be correlated with larger and more peripheral lesions.

Abbreviations: BCVA = best corrected visual acuity, ELISA = enzyme-linked immunosorbent assay, OT = ocular toxoplasmosis

Keywords: ocular toxoplasmosis, serology IgG IgM, acute chronic infection

INTRODUCTION

Toxoplasmosis is the most common cause of infectious posterior uveitis worldwide leading to severe vision loss,[1-4] although there is some evidence of decline in its prevalence in certain areas.[5] Ocular toxoplasmosis (OT) refers to eye disease related to infection from the obligate intracellular parasite *Toxoplasma gondii.*[6] In immunocompetent patients, this typically leads to recurrent posterior uveitis, which is characterised by unilateral, necrotizing retinitis with secondary choroiditis.[7] OT lesions can occur anywhere in the fundus and may be sight-threatening in cases where the posterior pole is involved.[8] These lesions tend to occur adjacent to a pigmented chorioretinal scar and can be associated with retinal vasculitis and vitritis.

In immunocompetent patients, toxoplasma-related retinochoroiditis is usually a self-limited infection and generally resolves spontaneously after a period or 4-8 weeks. However, treatment is recommended for lesions where there is a significant risk of visual loss; which includes lesions within the vascular arcades, adjacent to the optic disc, or larger than 2 optic disc diameters. OT is typically treated with tapering oral prednisolone, given with anti-microbial cover. Currently, there is a lack of high-level evidence to suggest which therapeutic regime is the most efficacious.

It can be very difficult to differentiate acquired OT from congenital disease based on clinical assessment alone. The absence of a previous scar favours the diagnosis of primary OT rather than recurrent disease, but there are exceptions to this rule. Although the diagnosis of OT is essentially clinical in most cases, the detection of toxoplasma antibodies can be helpful.[9, 10] Similar to most infections, the first antibodies to appear against Toxoplasma are Immunoglobulin M (IgM), usually within the first week following infection. IgM levels rise until their peak at 1-3 months,[11] then slowly decrease over the following 6 months, generally becoming undetectable after 6-9 months. However, IgM may remain detectable by Elisa linked immunosorbent assay (EIA) for up to 18 months.

An elevated titre of *T.gondii*-specific serum IgM antibody in the presence of negative IgG is regarded as a unique marker confirming the diagnosis of primary OT as a result of recent infection.[12] As cross-reactivity can occur with IgM tests, repeat serology may be performed to detect a rising IgG to confirm recent infection. In contrast, the presence of positive serum specific IgG antibody with negative IgM titre points to reactivation of a previous infection.[13] A literature search did not reveal any studies that have specifically described clinical differences depending on the result of serum IgM titre.

We hypothesised that there are phenotypic differences in the ocular characteristics using serum anti-toxoplasmosis IgM as a marker of recently

acquired disease. Therefore, the aim of this study was to examine differences in the clinical characteristics of OT according to their IgM status. Specifically, we explored and analysed the differences between the two groups in terms of demographics, clinical findings, intraocular inflammation, visual outcome, and the development of any complications.

PATIENTS AND METHODS

This was a retrospective study conducted in a single, high-volume uveitis tertiary referral practice in the United Kingdom from March 2011 to June 2018. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Moorfields Eye Hospital ethics committee (reference number CA18/UV/213).

Electronic pathology records of all patients attending Moorfields Eye Hospital from March 2011 to June 2018 were electronically searched in order to identify all patients with positive serum *T.gondii*-specific IgM tests, this was cross-referenced with the hospital pharmacy database for confirmation. Clinical notes were retrieved and reviewed in order to confirm the clinical diagnosis of OT. This formed the IgM+ group.

In order to obtain a comparison group, we also performed an electronic search of all pathology records in order to identify patients with positive OT with serum *T.gondii*-specific IgG tests, and negative IgM tests over the same period. Because this serological group of OT was much more prevalent, we randomly selected a comparator group that is twice as large as the IgM+ group in order to increase statistical power. Clinical records were retrieved and retrospectively reviewed.

Inclusion criteria specified that only the first presentation during the study period be analysed whilst all subsequent recurrences were excluded. In addition, a minimum of 6 months follow up was required for inclusion. By definition, all patients studied had toxoplasma IgM and IgG serology testing as part of their diagnostic investigations as it was by these criteria that we selected the patients from the hospital pathology records.

Clinical features at presentation including patient demographics, presenting symptoms, visual acuity, lesion size and location, presence or absence of a retinal scar and intraocular pressure were recorded. Outcome measures including visual acuity, anterior chamber and vitreous inflammation, and adverse events were recorded at 6 months.

Active lesion locations were divided into three zones as described previously.[14] Zone 1 is the region wherein most immediately sight-threatening lesions reside, and comprised of an area 2 disc diameters (3600μm) from the foveal center or 1 disc diameter (1800μm) from the margins of the optic disc (Figure 1). We subdivided zone 1 into three subareas: **A** central macula lesion involving fixation (central fovea); **B** lesion within 1 disc diameter from the margins of the optic disc; **C** lesion within arcades but not involving macula (extrafoveal). Zone 2-3 was defined as the area extending from the outer border of zone 1 to the ora serrata (outside arcades).

Serum IgM and IgG grouping

Patients were subdivided into two groups according to status of serum IgM at the time of presentation. Serologic criteria for the acute phase of systemic infection with *Toxoplasma gondii* included the presence of IgM antibodies, this group of patients was considered to have primary OT. In contrast, the chronic phase of systemic infection was defined as positive IgG antibodies (any titre) without IgM antibodies. Detection of IgG and IgM antibodies specific for *T.gondii* was performed using an ELISA test (Enzygnost Toxoplasmosis IgG and Enzygnost Toxoplasmosis IgM tests, Siemens Healthcare Diagnostics, Marburg, Germany) according to the manufacturer's instructions. Serological testing for IgG antibody was quantitative and the results were expressed in IU/ml, whereas testing for IgM antibody was categorical, and simply defined as IgM positive or negative. A level of greater than 3 IU/ml for specific IgG was considered positive.

Statistical analysis

Data was compiled onto a spreadsheet using Microsoft Excel 2016 (Microsoft Corp, Seattle, Washington). All visual acuity measurements were converted to LogMAR values for statistical analysis; very poor visions such as counting fingers or worse were converted to theoretical LogMAR values using previously validated criteria.[15] We examined the differences in demographic and clinical factors between the clinical groups defined according to IgM+ or IgM- status. Categorical data was analysed using Chi squared and Fisher's exact tests. Continuous distributions were first assessed for normality using the Shapiro-Wilk test. T-test and Mann-Whitney U test were used to compare normally and non-normally distributed variables respectively. Summary statistics were presented as mean ± standard deviation for normally distributed variables, and median (interquartile range) for non-normally distributed variables. Multinomial logistic regression was performed to assess whether age and IgM status were associated to lesion location. P values < 0.05 were considered statistically significant.

RESULTS

Patient demographics

For our study, 109 eyes from 106 patients were identified to have a confirmed diagnosis of ocular toxoplasmosis (OT) between March 2011 and June 2018. In three cases of bilateral disease, laterality of the study eye was randomised and the fellow eye excluded; as such, the final analysis included 106 eyes from 106 patients. In total, 50 females and 56 males were included in this study; minimum follow up was six months and maximum follow was 8 years (Table 1).

Clinical features, classified according to IgM status

Thirty-seven patients were positive in serum for toxoplasmosis IgM ("IgM+ group"), for all patients this was their first presentation of OT. Three patients (8.1%) were known to be immunocompromised, due to Good's syndrome, recent chemotherapy and immunosuppressive treatment (methotrexate and adalimumab) for inflammatory arthritis. In the other group, 69 patients tested negative for serum toxoplasmosis IgM ("IgM- group"). Two patients were immunocompromised due to HIV. Clinical features are henceforth described according IgM status and readers are referred to Table 2.

Patients in the IgM + group were significantly older than the IgM- group with a mean age difference of 17 years ($p < 0.0001$). There were no significant differences in gender or laterality of the affected eyes. On presentation, the commonest reported symptoms were blurred vision, floaters, and scotoma. The frequencies of these symptoms did not differ according to IgM status. Pain on presentation was present in a significantly higher proportion of the IgM- group than the IgM+ group (20.3% vs 2.7%, $p=0.017$).

Retinal scars were observed in a very small minority of the IgM+ group compared to the majority of the IgM- group (8% vs 88%, $p<0.0001$, Table 2). On review of these cases, all three cases within the IgM+ group demonstrated mild scarring which surrounded an active lesion

There were significant differences in the location of retinal lesions between the IgM+ and IgM- groups ($p=0.012$, Table 2). In the IgM+ group, central lesions affecting the macula area (zone 1A) were present in 12 patients; whereas in the IgM- group, macula lesions were noted in 8 patients (32% vs 12%). Conversely, there were fewer lesions far from the macula area or optic nerve (zone 1C) but within the arcades in the IgM+ group as compared to the IgM- group (3% vs 23%). The proportion of retinal lesions adjacent to the optic disc (zone 1B) was similar in the two groups (16% vs 17%), as were peripheral retinal lesions (zones 2-3, 49% vs 48%, Table 2).

Out of the 51 patients (combined IgM+ and IgM- groups) who presented with toxoplasmosis lesions outside of the major vascular arcades, the majority of

lesions were located in either the superotemporal (28/51, 55%) or superonasal (16/51, 31%) quadrants. Fewer lesions were present in the inferotemporal (6%) and inferonasal quadrants (8%), this difference was statistically significant ($p < 0.001$). Lesion location did not differ between IgM+ and IgM- groups ($p = 0.78$).

Logistic regression showed that zone 1 involvement was negatively correlated with age (Odds ratio: 0.95, $p=0.007$), but not affected by IgM status ($p=0.12$). In other words, patients with lesions within zone 1 were significantly younger in both IgM+ (45.8±15.5 vs 55.8±13.7, $p=0.045$) and IgM- (30.9±12.4 years vs 37.8±10.2, $p=0.014$) groups. Furthermore, lesion size tended to be larger in older patients ($p=0.003$); but was not influenced by IgM status ($p=0.83$).

Visual acuity (VA)

Mean LogMAR visual acuities were compared between the group at presentation, 3 months, 6 months, and final acuity. Although no significant differences were found, we noted that the presenting VA tended to be better in the IgM+ group compared to the IgM- group at presentation, but that this was reversed at the end of the treatment period. Further analysis demonstrated that the visual improvement in LogMAR acuity following treatment was significantly larger in the IgM- group (0.15 (0.00 – 0.50) vs 0.30 (0.07 – 0.80), $p=0.018$, Table 3).

Anterior chamber and vitreous inflammation

Table 3 summarises the clinical assessment of anterior chamber and vitreous activity at presentation and 6 months follow up. At presentation, The IgM- group presented with significantly more AC ($p = 0.0087$) and vitreous ($p = 0.045$) inflammation than the IgM + group. However at 6 months, there were no statistically significant differences between the two groups ($p = 0.51$).

Complications

The prevalence of vision impairing complications including choroidal neovascularisation, epiretinal membrane, retinal tear, rhegmatogenous retinal detachment (RRD), cystoid macular oedema and retinal vein occlusions are shown in Table 4. Overall, the difference in overall rate of complications between IgM+ and IgM- groups was not statistically significant (24% vs 15%, $p=0.21$). On comparison of individual complications, RRD occurred more frequently in the IgM+ group as compared to the IgM- group which was statistically significant (4/37 vs 1/69, $p = 0.049$).

Treatment

Treatment for the first attack of OT was given in all IgM+ patients and in 57 out of the 69 IgM- patients. To be included in the antiparasitic treatment groups, the drugs had to be administered for at least 4 weeks. In the IgM+ group, 28

out of the 37 patients (75.67%) were treated with azithromycin whereas 9 out of the 37 had treatment with sulfadiazine (24.32%). In this group, 22 of the patients received a concomitant antiparasitic drug pyrimethamine, following our center’s protocol.

DISCUSSION

Clinical examination is the standard diagnostic method for OT. However, in the majority of cases, para-clinical methods may prove to be valuable in confirming the disease. Serological tests, mainly anti-Toxoplasma IgM and IgG levels, are the basis of serodiagnosis and differentiation between the acute and chronic/reactivated forms of OT. According to many published studies, patients with positive IgM and/or low IgG avidity are considered as acutely acquired cases (usually defined as acquisition of infection in recent 6 months) whereas patients with negative IgM and positive IgG are considered as chronic/reactivated cases. In our daily practice, serological tests are requested in all cases along with the suspected clinical picture.

In this study we present a large series of patients with OT and compared the clinical characteristics according to IgM status. To summarise our results, the IgM+ group were markedly older, had larger lesions, and had a higher prevalence of macular involvement. We also found age to be correlated with larger lesions and macular involvement when analysing the data as a whole.[16] In addition, the IgM- group had significantly greater levels of intraocular inflammation at presentation.

Pain on presentation was present in a significantly higher proportion of the IgM- group and this is likely to be explained by the fact that IgM- cases have more intense AC inflammation. Intense AC inflammation might occur secondary to retinochoroiditis near the ora serrata, which may lead to more pain. The more severe inflammation might also be related to other, as yet unknown, parasite-related or host-related factors.

In the group of IgM- patients, the mean age at presentation was 34.1 years, which was similar to previous reports.[17, 18] This serologic phase of the disease is far more common than the acute stage. Our observation that IgM+ patients were older might be attributed to the decline of cell-mediated immunity in the elderly. Researchers in the Netherlands, for example, have found that most patients with ocular toxoplasmosis who have serologic evidence of recent infection are older. [19-21]

This study did not include a control group of IgM+ cases without ocular involvement to establish a comparison related to age and disease behavior, but a possible explanation is that older patients acquiring the disease for the first time (IgM+ cases) are more likely to develop eye involvement than younger patients. Positive serum IgM is a relatively reliable marker for the acute phase reaction occurring as a result of first-episode disease acquisition. Unfortunately, serum IgM data in certain cohorts are still lacking; consequently, the frequency of ocular involvement in post-natally acquired toxoplasmosis infection currently remains unknown.

Patients in this study received antibiotic treatment according to trust protocol.

Our current local treatment protocol does not make a distinction between IgM status; as a result, both groups received comparable treatments. It should be noted that a recent Cochrane review highlighted a lack of current available evidence to support antibiotics use in OT.[22] Given the significant differences in the IgM+ and IgM- groups found in the present study, we suggest that this distinction be made during any future clinical trials.

In our series, macular involvement was more common in the IgM+ group. However multivariate analysis showed that this could be accounted for by young age, rather than IgM status per se. Several reasons have been argued for the preference of toxoplasmic ocular lesions at the macular area. There are some data to suggest that the location of lesions does not occur as a random event. Mets and associates [23] showed that 52 of 89 (58%) newborns with congenital *T. gondii* infection and ocular disease had macular lesions. This figure is substantially higher than the number expected if lesions were distributed randomly, especially when the fact that the anatomic macula comprises only approximately 5% of the total retinal area is taken into consideration. Anatomic and microvascular differences between the macular and the peripheral retina might create a microenvironment that can influence the location of lesions following either congenital or post-natally acquired infections.[24] Finally, a study of post-mortem eyes from individuals with no known ocular disease or immune systemic dysfunction showed that macrophages, which participate in host defenses against *T.gondii* infection, were significantly less common in the macula area than in the peripheral retina.[25]

We hypothesise that in IgM+ ocular toxoplasmosis, there is systemic parisitaemia arising from recently acquired infection. The macula has proportionately the highest blood supply and this might explain the predilection for macular involvement.

We observed that IgM+ patients typically did not have co -existing retinal scars at presentation, as we would not expect to see retinal scars in a primary infectious process. In three cases (8%) where scars were observed, these were non-pigmented and adjacent to active lesions. As such, it is possible that the lesions which generated the non-pigmented scars may resolve within 12 months, during which time IgM can remain positive.

One further observation from our study was that IgM+ patients had less AC inflammation and vitreous inflammation at presentation when compared with IgM- patients. We postulate two possible explanations. Firstly, the IgM+ patients were on average older – immune-senescence with age may mean that these patients do not mount such an exuberant immune response. Secondly, IgM- patients by definition have already been immune-primed as their disease results from reactivation, and a primed immune system will lead to a more

severe and rapid onset host inflammatory reaction. But, as we would predict, the duration of inflammation subsides faster in the primed immune system of the IgM- group compared to the IgM+ group. This explains the greater levels of anterior chamber inflammation at 6 months in the IgM+ group.

In terms of complications between the groups, our analysis is limited by sample size. Whilst we could find no significant difference in total complications, we did find that the IgM+ group had a significantly higher rate of rhegmatogenous retinal detachment. The reason for this is unknown but we postulate that the older ages of the IgM+ group is a possible contributing factor. Studies of spontaneous rhegmatogenous retinal detachment (RD) show much higher rates of RD in the 50-60 year old range versus the 30-40 age group.[26] This type of RD was associated with a posterior vitreous detachment. Although we are extrapolating from this data to RD associated with a toxoplasma related ocular inflammatory disease, both share the same underlying pathogenesis. We postulate that vitritis associated with toxoplasma causes PVD with subsequent vitreous-retinal traction causing retinal breaks and RD, which would be more likely with increasing age.

In summary, our findings suggest that recently acquired ocular toxoplasmosis, as defined by positive serum IgM, occurs in older patients, and results in greater visual morbidity, as evidenced by the significantly poorer visual recovery at 6 months when compared to IgM negative patients. This is most likely due to the greater preponderance of macular involvement. In addition, these patients had a higher proportion of retinal detachment as compared to the IgM negative group.

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TABLES

Table 1: Patient demographics

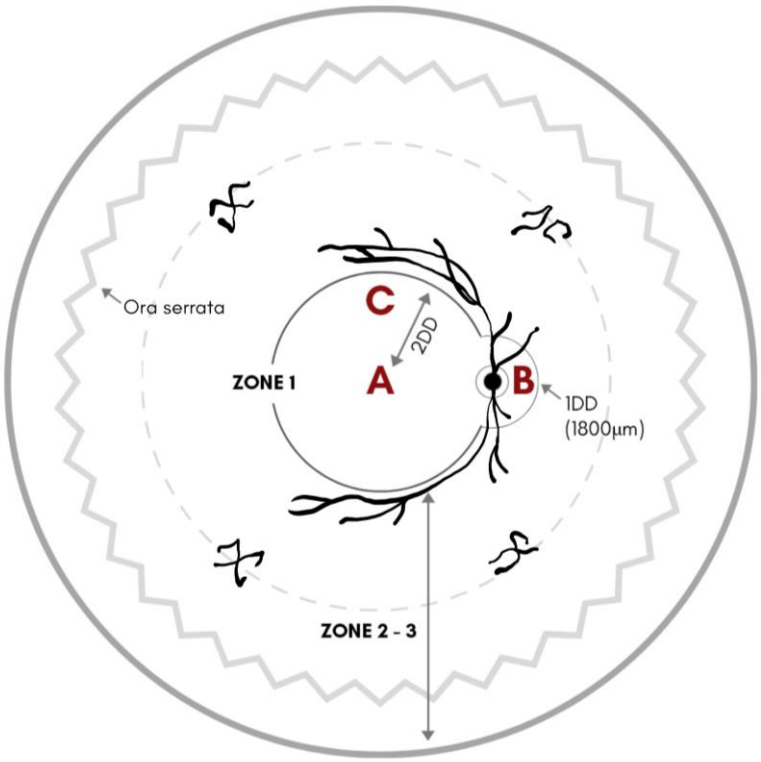
		IgM+	IgM-	Total	P value
Number		37	69	106	
Age		51.1 ± 15.3	34.1 ± 11.8	40.1 ± 15.4	<0.0001
Gender	Male	18 (49%)	38 (55%)	56 (53%)	
	Female	19 (51%)	31 (45%)	50 (47%)	0.55
Laterality	Right	16 (43%)	32 (46%)	48 (45%)	
	Left	21 (57%)	37 (54%)	58 (55%)	0.84
Immunocompromised		3 (8%)	2 (3%)	5 (5%)	0.34
Presenting symptom	Blurred vision	21 (57%)	46 (67%)	67 (63%)	0.40
	Scotoma/visual field defect	4 (11%)	6 (9%)	10 (9%)	0.74
	Pain	1 (3%)	14 (20%)	15 (14%)	0.017
	Floaters	9 (24%)	19 (28%)	28 (26%)	0.82

Table 2: Features at presentation

			IgM+	IgM-	Total	P value
Number			37	69	106	
Size of Lesion		≤1DD	13 (35%)	37 (54%)	50 (47%)	
		1-2 DD	15 (41%)	19 (28%)	33 (31%)	
		> 2DD	9 (23%)	12 (17%)	21 (20%)	0.21
Lesion location	**Zone 1**	**A**. Macula	12 (32%)	8 (12%)	20 (19%)	
		B. <1DD of optic disc	6 (16%)	12 (17%)	18 (17%)	
		C. Within arcades	1 (3%)	16 (23%)	17 (16%)	
	Zone 2-3	Outside of arcades	18 (49%)	33 (48%)	51 (48%)	0.012
Lesion quadrant if outside of arcades		Superotemporal	11 (61%)	17 (52%)	28 (55%)	
		Superonasal	5 (28%)	11 (33%)	16 (31%)	
		Infratemporal	1 (6%)	2 (6%)	3 (6%)	
		Infranasal	1 (6%)	3 (9%)	4 (8%)	0.78
Scar noted at presentation			3 (8%)	61 (88%)	64 (60%)	<0.0001
IOP at presentation*			17 (14 – 23)	17 (14 – 26)	17 (14 – 25)	0.92

*Values for IOP are presented as median (interquartile range);
IOP: intraocular pressure.

Figure 1: Description of lesion location
DD: disc diameter



Zone 1

A: central macula lesion involving fixation (central fovea)

B: lesion within 1 disc diameter from the margins of the optic disc

C: lesion within arcades but not involving macula (extrafoveal)

Zone 2-3: outside arcades

Table 3: Visual acuity and intraocular inflammation

		IgM+	**IgM-**	**P value**
Visual acuity*	At presentation	0.50 (0.10 – 0.75)	0.40 (0.00 – 1.00)	0.71
(LogMAR)	3 Months	0.20 (0.00 – 0.30)	0.20 (0.00 – 0.60)	0.70
	6 Months	0.00 (-0.10 – 0.20)	0.00 (0.00 – 0.30)	0.51
	Final	0.20 (-0.10 – 0.30)	0.00 (-0.10 – 0.30)	0.17
	Improvement	0.15 (0.00 – 0.50)	0.30 (0.07 – 0.80)	0.018
AC inflammation at presentation	0-1	24 (65%)	26 (38%)	
	≥2	13 (35%)	43 (62%)	**0.0087**
AC inflammation at 6 months	0	21 (72%)	58 (88%)	
	≥1	8 (28%)	7 (11%)	0.064
Vitreous inflammation at presentation	0-1	22 (59%)	27 (39%)	
	≥2	15 (41%)	42 (61%)	0.045
Vitreous inflammation at 6 months	0	20 (80%)	55 (87%)	
	≥1	5 (20%)	8 (13%)	0.51

*Values for visual acuity are presented as median (interquartile range); AC, anterior chamber.

Table 4: Adverse events and recurrence

		IgM+	**IgM-**	**Total**	**P value**
Adverse events	CNV	0 (0%)	1 (1%)	1 (1%)	1.0
	ERM	3 (8%)	2 (3%)	5 (5%)	0.34
	Retinal Tear	1 (3%)	2 (3%)	3 (3%)	1.0
	RRD	4 (11%)	1 (1%)	5 (5%)	0.049
	CMO	1 (3%)	0 (0%)	1 (1%)	0.35
	RVO	0 (0%)	4 (6%)	4 (4%)	0.30
	Overall	9 (24%)	10 (15%)	19 (18%)	0.21
Recurrence		6 (16%)	23 (33%)	29 (27%)	0.07

Time to recurrence* (years)		4.34 (0.28 – 6.08)	1.40 (0.82 – 2.08)	1.41 (0.82 – 3.39)	0.15

*Values for time to recurrence are presented as median (interquartile range); AC, anterior chamber. CNV, neovascular membrane; ERM, epiretinal membrane; RRD, rhegmatogenous retinal detachment; CMO, central macular oedema; RVO, retinal vein occlusion.