Purpose: The aim of this study was to provide a retrospective analysis of the presentation, demographics, and treatment regimens for ocular toxoplasmosis at a large tertiary referral uveitis center.

Design: Retrospective cohort study.

Participants: A total of 48 patients with ocular toxoplasmosis who presented to Sydney Eye Hospital participated in this study. Studies comparing antimicrobial therapy and observation are limited. Significant controversy remains, even among uveitis experts, regarding which treatment is most efficacious to treat acute OT. Data on clinical features, treatment, and prognosis in the Asia Pacific region are also limited. This study is a retrospective review of the clinical features, treatment regimens, and outcomes at a single tertiary referral uveitis center in Sydney.

Ocular Toxoplasmosis in a Tertiary Referral Center in Sydney Australia—Clinical Features, Treatment, and Prognosis

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The classic therapy for OT consists of pyrimethamine, sulfadiazine, and oral corticosteroids with folinic acid to minimize myelosuppression from pyrimethamine. Alternative antimicrobial treatment regimens include: systemic clindamycin, azithromycin, atovaquone, spiramycin, tetracycline, clarithromycin, and combination of trimethoprim and sulfamethoxazole.8 Given the remitting natural history of OT in immunocompetent hosts and the morbidity involved with antimicrobial treatment, there are arguments for watchful waiting instead of active treatment in patients with nonvision-threatening ocular disease.8 Studies comparing antimicrobial therapy and observation are limited. Significant controversy remains, even among uveitis experts, regarding which treatment is most efficacious to treat acute OT. Data on clinical features, treatment, and prognosis in the Asia Pacific region are also limited. This study is a retrospective review of the clinical features, treatment regimens, and outcomes at a single tertiary referral uveitis center in Sydney.

METHODS

Study Design and Population

All patients seen by the Uveitis service at the Sydney Eye Hospital from January 2007 to December 2016 were included in...
this study. Patients were diagnosed with OT and potentially included in the study based on clinical features and the diagnosis of OT was made by a uveitis subspecialist. Clinical diagnosis was based on criteria formulated by Holland and further elucidated in other large toxoplasmosis cohort studies. Ancillary ophthalmic testing including optical coherence tomography, fundus auto-fluorescence, and fundus fluorescein angiogram were performed as clinically indicated based on features and media clarity. Toxoplasmosis serology was not routinely performed unless this was the first presentation of uveitis or chorioretinitis or if the patient was pregnant or peripartum. Baseline investigations for initial presentation included: full blood count, syphilis serology, tuberculosis testing (chest X ray and or QuantiFERON gold) as well as toxoplasmosis serology (IgG and IgM). If the diagnosis was uncertain, a diagnostic vitreous sample was taken and sent for toxoplasmosis conventional polymerase chain reaction (PCR) testing for T. gondii DNA using PCR primers for T. gondii specific B1 gene. The choice of antimicrobial agent was by clinician preference. Patients with posterior pole involvement often received triple therapy.

This study was conducted within the tenants of the Declaration of Helsinki with area health service ethics approval.

Data Collection

A retrospective review of all patient files with a diagnosis of OT was conducted. Data collected included: baseline demographics, country of birth, ethnicity, ocular scars consistent with previous OT, pregnancy status, and evidence of an acquired or congenital immunodeficiency. Visual acuity was converted to logMAR. Intraocular inflammation was graded using the Standardization of Uveitis Nomenclature (SUN) classification and the intraocular pressure (IOP) was recorded. The location of the lesion was recorded in terms of proximity to the macula or optic nerve. Large or extensive lesions were defined as >3 disc diameters as defined by previous studies. Treatments including: topical anti-inflammatory therapy, IOP lowering therapy, antimicrobial therapy, and oral corticosteroids were recorded. Adverse events associated with any therapy were recorded.

Patients were reviewed at presentation, during treatment and post treatment. Those without complications were discharged and asked to return if symptoms returned. Relapses were defined as signs of active uveitis after a minimum of 3 months of inactive uveitis off treatment.

Statistical Analyses

Data analysis was conducted using SPSS (IBM). Demographics and characteristics were recorded. Visual acuity was converted to logMAR for statistical purposes. Data that did not conform to normality were analyzed using nonparametric tests. Paired sample tests were conducted using the Wilcoxon signed rank test and for independent comparisons a Mann-Whitney U test was performed. Relapse rates were calculated as person-years to account for variable patient follow-up.

RESULTS

Patient Demographics

Forty-eight patients were diagnosed with OT during the study (48 out of 1165 patients). This accounted for 20% of the infectious uveitis presenting to the center. Two patients were excluded after further investigations revealed other diagnoses including Multiple Evanescent White Dot Syndrome (MEWDS) and Coats disease. Demographic features are presented in Table 1. Mean follow-up was 1.8 years (SE 0.34). There was no statistical difference in the vision loss between those born in Australia and those born overseas (P = 0.74). The majority of patients were immunocompetent (n = 38) with only 4 patients having an acquired immune deficiency such as: hematological malignancy, end stage renal failure and use of systemic immunosuppressive medications. There were 2 patients who were either pregnant or peripartum at first presentation of OT. In both patients the serology was consistent with reactivation (IgG positive and IgM negative). Three of the four patients who had a vitreous sample taken for PCR were positive for toxoplasmosis (75%).

Sixteen patients had evidence of chorioretinal scarring consistent with previous ocular toxoplasmosis. Eleven patients were aware of a previous episode. Serologic testing was conducted on 15 patients (36%). The majority of these had a positive IgG and one patient had a positive IgM.

Characteristics of the Chorioretinitis

All cases of OT were unilateral. The visual acuity on presentation was logMAR 0.51 (6/19) (SE 0.096) and improved
Evidences of previous scarring.

with their first episode of ocular toxoplasmosis and those who had extensive retina lesions (within 1 disc diameter). There were 10 patients with evidence of panuveitis with both vitritis and anterior chamber activity. There was no statistical difference using the location of the lesion (P = 0.74) or final visual acuity (P = 0.8) between patients with their first episode of ocular toxoplasmosis and those who had evidence of previous scarring.

Treatment

The majority of patients in this cohort were treated with oral prednisolone and antimicrobial therapy. Patients also received topical corticosteroids and IOP-lowering medication as needed to control anterior chamber cells and IOP. No patients were treated with oral prednisolone alone. Patients with diagnostic uncertainty based on examination either due to first presentation with no evidence of chorioretinal scars or atypical chorioretinitis (n = 13) were initially started on antimicrobials and the addition of prednisolone was included at the first review once results had been observed without treatment. There was a relapse within 1 year which required antimicrobial therapy (Table 4).

Three patients were started on secondary sulfamethoxazole and trimethoprim prophylaxis; 2 of these patients were immunocompromised. Three (75%) immunocompromised patients had per oral (PO) prednisolone therapy during their course of antimicrobial treatment however, 2 at a lower dosage. One patient who was critically ill with sepsis did not have PO corticosteroids but was investigated with neuroimaging to exclude cerebral toxoplasmosis in consultation with the infectious disease physicians. This patient was given intravitreal clindamycin.

Relapses

Thirteen patients had at least 1 relapse with 4 patients having >1 relapse. The time to recurrence was 2.2 years (SE 0.45) and the rate of relapse was 0.09/person-years of follow-up (Fig. 1).

The majority of relapses were within or adjacent to a previous chorioretinal scar (n = 16). Two immunocompromised patients experienced a relapse despite prophylaxis with sulfamethoxazole and trimethoprim.

Outcomes

The majority of patients (n = 32) made a visual recovery of logMAR 0.2 (6/9). Of patients who developed severe vision loss logMAR 1.0 (≤6/60) (n = 7), 3 patients had macula scarring, 2 patients developed occlusive retinitis and cystoid macular edema, 1 developed a central retinal vein occlusion, and 1 developed a submacular hemorrhage secondary to a choroidal neovascularization. Of these patients, 2 required retinal laser. No patients required cataract surgery during the period of observation.

Adverse Effects of Therapy

Treatment was well tolerated. Two diabetic patients developed elevated blood glucose levels from oral steroid therapy and required augmented diabetes treatment and 1 patient developed new-onset type 2 diabetes during prednisolone treatment. Two patients treated with clindamycin developed significant

| Characteristic                  | n (%)       |
|--------------------------------|-------------|
| **Visual acuity**              |             |
| Presentation                   | 0.51 (SE 0.096) |
| Last follow-up                 | 0.31 (SE 0.094) |
| IOP                           | 18 (SE 1.54) |
| **Anterior cells**             |             |
| 0                              | 6 (13)      |
| 0.5+                           | 9 (19)      |
| 1+                             | 38 (31)     |
| 2+                             | 6 (13)      |
| 3+                             | 9 (19)      |
| **Vitritis**                   |             |
| 1+                             | 26 (54)     |
| 2+                             | 11 (23)     |
| 3+                             | 9 (19)      |
| 4+                             | 2 (4)       |

IOP indicates intraocular pressure.

TABLE 3. Location of Retinitis at Presentation in Patients With Ocular Toxoplasmosis

| Location Of Retinal Lesions | n (%) |
|-----------------------------|-------|
| Within vascular arcades     |       |
| Macular                     | 9 (19) |
| Adacent to optic nerve*     | 9 (19) |
| Other central location      | 26 (60) |
| Peripheral                  | 26 (54) |
| Both central and peripheral | 10 (21) |
| Extensive retina lesions    | 4 (8)  |

*Within 1 disc diameter.

TABLE 4. Treatment of Ocular Toxoplasmosis Including Topical and Systemic Modalities

| Treatment Modalities               | n (%) |
|------------------------------------|-------|
| Topical anti-inflammatory           | 18 (38) |
| PO prednisolone                    | 42 (88) |
| Antimicrobial therapy              |       |
| Clindamycin                        | 34 (70) |
| Pyrimethamine + sulfadiazine       | 7 (15)  |
| Trimethoprim/sulfamethoxazole      | 4 (8)  |
| Other                              | 2 (4)  |
| No treatment                       | 1 (2)  |
| Intraocular clindamycin            | 1 (2)  |
| Topical ocular IOP-lowering therapy| 6 (13) |

IOP indicates intraocular pressure; PO, per oral.
gastrointestinal symptoms requiring cessation of therapy but were not changed to another antimicrobial as they near the completion of therapy. No patients developed *Clostridium difficile* colitis as a result of antimicrobial therapy.

**DISCUSSION**

This study describes the clinical features and treatment regimens utilized at a large tertiary uveitis center in Sydney, Australia. The demographics are diverse with a number of patients born overseas, and some from toxoplasmosis endemic areas such as Latin America and the Middle East. The proportion of uveitis caused by OT in our cohort was 3% (48/1165). This is lower compared to other studies locally in Australia and internationally. A study in central Australia reported 82% of posterior uveitis and 60% of all uveitis (both anterior and posterior) in their indigenous cohort were presumed to be secondary to OT. The proportion of uveitis thought to be due to *T. gondii* in other case series ranged from 4.2% (80/1916) in a German cohort to 12% (154/1300) in a Dutch cohort. The variation in prevalence of OT observed in all these studies is likely due to the complex interactions between environmental factors, socioeconomic status, and dietary habits of the human host in the pathogenesis of OT. Additionally, there is significant referral bias in the patient population referred for diagnosis and management to the major tertiary referral eye center for New South Wales.

The visual prognosis in our cohort was better than other larger studies. Bosch-Driessen et al. examined a cohort of 154 patients and found that 37 (24%) developed blindness (6/60 or 20/200). In our study 16% of patients developed severe vision loss with macula involvement and scarring being the most common cause. Recurrences occurred less frequently than other studies at 31%. This may be due to the small proportion of immunocompromised hosts (4/48) in our cohort and the distribution of the milder genotype of *T. gondii* (type II) within Australia. In our cohort there was no statistically significant difference between the vision loss and the country of origin. The severity and relapse rates of OT are largely dependent on the host immunity and the genotype of the parasite. There are 3 major genotypes (type I, type II, and type III) and genotype II, which is most common in Australia, is typically less virulent, causes milder disease, and associated with lower rates of relapse.

 Diagnosis was based on clinical examination in this cohort. Serological testing was not routinely conducted and in contrast to the recommendations outlined by Robert-Gangneux and Darde serological testing was only used if this was the first presentation of uveitis in the absence of previous toxoplasmosis chorioretinal scars or the patient was peripartum. PCR on vitreous samples helped facilitate the diagnosis in 3 of 4 patients who had sight threatening disease and an unclear clinical picture. However, 1 patient with acquired immunosuppression had a negative result; however, clinically it was determined that OT was the most likely cause. This is consistent with literature regarding the diagnostic utility of vitreous PCR for OT. The majority of patients in this cohort were not immunocompromised and those who were had atypical presentations including minimal vitritis, anterior chamber activity, and larger lesions on fundoscopy. Only 2 patients in this sample were pregnant or peripartum.

There is great variation in treatment approaches between uveitis specialist centers globally which may be due to differences in disease severity due to organism differences or clinical variation. There are sound arguments for watchful waiting in an immunocompetent patient with small peripheral lesions and/or low-grade overlying inflammatory response as OT is a self-limiting disease and there is treatment-related drug toxicity. In this study, only 1 immunocompetent patient with minimal clinical disease was observed and not treated with antimicrobial therapy, and this patient had a relapse within 1 year of presentation necessitating the use of antimicrobial therapy. The referral bias in the population managed at Sydney Eye Hospital is such that nearly all patients with ocular toxoplasmosis required treatment with antimicrobial drugs and oral corticosteroids. Systemic clindamycin was the most commonly used antimicrobial because of its accessibility, low cost, low risk of drug toxicity, and safety in pregnancy and breastfeeding, compared with other treatment regimens. Sulfadiazine can only be accessed via an Australian government-controlled special access scheme. Pyrimethamine can cause myelosuppression and requires regular full blood count monitoring. Sulfadiazine not uncommonly causes severe allergic reactions. Thus, pyrimethamine and sulfadiazine were reserved...
for those with macula threatening disease using guidelines from previous studies with regular monitoring for blood dyscrasias and liver dysfunction monitored. Azithromycin and combination trimethoprim and sulfamethoxazole are not funded by the Australian pharmaceutical benefit scheme for treatment of OT. Systemic corticosteroids were only used in conjunction with systemic antimicrobial therapy. In the present study, clindamycin was well tolerated and could be an alternative antimicrobial to triple therapy antimicrobial agent for treatment of OT in Australian-acquired diseases where genotype II is predominant. In Australia, clindamycin is widely available, and in this small cohort there were no severe adverse events. There are limited data on head-to-head trials comparing outcomes of systemic clindamycin monotherapy versus combination pyrimethamine and sulfadiazine combination therapy. Rothova et al demonstrated pyrimethamine–sulfadiazine more commonly resulted in a marked reduction in lesion size (>0.5 disc diameters) more frequently than clindamycin (49% vs 28%). Adverse effects experienced in the pyrimethamine group was 52% including leucopenia, rashes and fevers. Tabbara et al compared clindamycin monotherapy versus clindamycin and sulfadiazine combination therapy in a small cohort of 17 patients and found that the combination arm had minimal benefit in outcome with 4 days faster resolution of visual symptoms.

Intravitreal clindamycin and oral corticosteroids have been demonstrated to be noninferior to systemic therapy of pyrimethamine and sulfadiazine with corticosteroids in 2 randomized controlled trials. This indicates that clindamycin has some efficacy for treating OT and the advantage of intravitreal clindamycin over systemic clindamycin is the much higher ocular tissue concentration. Systemic clindamycin concentrates well in ocular tissue and can penetrate the parasite cyst wall and is a reasonable choice of antimicrobial therapy for OT. In this study, only 1 patient was treated with intravitreal clindamycin at the time of the vitreous tap; however, the visual acuity outcome was poor due to macular fibrosis and atrophy.

Systemic antimicrobial prophylaxis was not routinely used and is typically reserved for patients who are immunocompromised or those with only 1 functional eye and frequent recurrences. The agent of choice is sulfamethoxazole and trimethoprim. There were relapses in the 2 immunocompromised patients treated prophylactically and included in this study. This study is limited by its small size, retrospective nature, and the referral bias in the study population. Additionally, patients are discharged from the uveitis service once their acute episode has resolved unless there are complications such as elevated IOP. Some patients with relapses may have presented to another eye center. There is likely to be insufficient statistical power to identify important variables influencing outcomes. Similarly, this study is too small to offer recommendations into diagnostic investigations used in the cases of diagnostic uncertainty involved OT.

Despite these limitations, this study is one of the largest samples collected in Australia to date and demonstrates that incidence of OT in Sydney is lower, and disease severity milder than that seen in other parts of the world, resulting in fewer recurrences and less severe vision loss. The real world data from this study are important in helping ophthalmologists to manage a relatively uncommon disease with significant potential to damage vision in predominantly young, productive adults.

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