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Outcome of Macular Toxoplasmosis

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Abstract

Objective: To assess the structural and functional outcome of macular toxoplasmosis in a cohort of immunocompetent patients following treatment with antimicrobial agents and steroids.

Methods: The medical records of 12 consecutive immunocompetent patients who presented to The Eye Center, Riyadh, Saudi Arabia between 2001 and 2011 with acquired primary or recurrent macular toxoplasmosis were retrospectively reviewed. All patients filled a comprehensive uveitis questionnaire and underwent complete eye examination including visual acuity testing, funduscopy, OCT of macula, fundus photos and fluorescein angiography when indicated. Blood was drawn for toxoplasma antibodies and for other serologic work-up. All patients received systemic antimicrobial therapy in combination with corticosteroids. Structural (macular morphology) and functional (visual acuity) response to treatment was assessed and patients were followed up for a mean period of 6 months.

Results: There were 8 male and 4 female patients with mean age of 34 years (range, 16-54 years). All patients showed clinical evidence of improvement in visual acuity and healing of toxoplasmic retinochoroiditis within the first 4 weeks of therapy and at 6 months follow-up. Nine patients (75%) had 20/40 visual acuity or better at 6 months. Ten (83%) out of the 12 patients had a residual macular scar affecting their final vision. Two patients (17%) who presented early and received treatment within 24 hours of symptoms onset had full resolution of the retinochoroiditis without macular scarring and regained normal vision.

Conclusion: Prompt treatment in macular toxoplasmosis may preserve vision threatening structures and lead to good visual outcome.

Keywords: *Toxoplasma gondii*; Ocular toxoplasmosis; Panuveitis; Retinochoroiditis; Posterior uveitis; Macular scar

Introduction

Ocular toxoplasmosis is caused by the obligate intracellular parasite *Toxoplasma gondii*. The disease may be congenital or acquired and remains one of the most common causes of infectious posterior uveitis in immunocomptent individuals [1,2]. Macular lesions are more commonly seen in eyes with congenital disease [2]. Little has been reported about the course and outcome of acquired macular toxoplasmosis.

Healing of the toxoplasmic retinochoroiditis is usually associated with retinal pigment epithelial proliferation and scar formation. Retinochoroiditic scars may harbor the encysted form of the parasite which may last for years and sometimes decades. Rupture of the cyst may lead to recrudescence of the infection in the retina [1]. Damage to the retinal layers and disruption of the architecture of the retina may be caused by the proliferating organism itself or by the induced inflammatory reaction. Lesions affecting the macula are usually associated with cystoid or diffuse macular edema and the inflammatory response may lead to damage of the photoreceptors in the macular area. Macular lesions, therefore, may cause early symptoms and rapid loss of central vision. A residual macular scar after the retinichoroiditis resolves remains a major complication of the disease and usually results in permanent visual loss.

Although treatment with antimicrobial agents may lead to containment of the parasite and prevention of its replication in the retinal layers, the inflammatory response associated with toxoplasmic infection may lead to damage of the innocent bystander tissue of the retina and choroid. In such situations, the use of the antimicrobial agents alone may not be sufficient to prevent damage of visually important structures. Systemic and intraocular steroids have been previously used in patients with ocular toxoplasmosis [1,3-5]. The fear of suppressing the defense mechanisms of the host has limited the use of periocular injections of steroids [6]. Under antimicrobial coverage, corticosteroids may suppress the acute inflammatory response, expedite the resolution of macular edema, and consequently inhibit or limit the damage of the retinal cells.

The main objective of this study is to assess the structural and functional outcome of acquired macular toxoplasmosis in

immunocompetent patients following treatment with systemic antimicrobial agents and steroids.

Patients and Methods

The medical records of 12 consecutive immunocompetent patients who presented to The Eye Center, Riyadh, Saudi Arabia between 2001 and 2011 with acquired primary or recurrent macular toxoplasmis were reviewed. Macular toxoplasmsis was defined as lesions affecting or involving the macula (anatomic fovea centralis) which is located approximately 3 mm temporal to the optic disc and is about 1.5 mm, or one disc size, in diameter [7,8]. Each patient underwent complete ophthalmologic examination including:

(1) Visual acuity assessment at presentation, four weeks and 6 months after treatment,

(2) Funduscopy and fundus photographs, during and after treatment,

(3) Optical coherence tomography (OCT) at presentation, 4 weeks and 6 months

All patients were treated with systemic antimicrobial agents in combination with systemic or periocular steroids and were followed up over a mean period of 6 months. Table 1 lists all the patients included in this study.

Patients	Age/Sex	VA at Presentation	VA at 1 month	VA at 6 months	Symptoms to presentation duration	Residual macular scar
1	38/F	CF 1F	20/30	20/30	1 week	Yes
2	54/M	CF 5F	20/200	20/60	20 days	Yes
3	45/F	20/40	20/25	20/25	6 days	Yes
4	27/M	20/400	20/35	20/35	2 weeks	Yes
5	16//M	CF 3F	CF 5F	20/400	3 weeks	Yes
6	50/M	CF 2F	20/30	20/40	5 weeks	Yes
7	50/M	CF 2F	20/60	20/30	9 days	Yes
8	38/F	CF 2F	20/200	20/25	15 days	Yes
9	18/F	20/120	20/50	20/25	5 days	Yes
10	42/M	CFNF	20/400	20/400	6 weeks	Yes
11	16/M	20/200	20/20	20/20	9 hours	No
12	25/M	CF3F	20/25	20/16	14 hours	No

VA: Visual Acuity; CF: Counting Fingers; CFN: Counting Fingers Near Face; F: Foot/Feet.

Table 1: Twelve patients with macular toxoplasmosis before and after treatment.

The study was approved by the Institution Review Board. The authors, herewith, state that all applicable institutional and governmental regulations were followed during this study.

Diagnostic criteria

The diagnosis of macular toxoplasmic retinochoroiditis was established by (1) the presence of macular infiltrate(s) surrounded by edema with overlying vitritis and adjacent vasculitis, with or without retinal necrosis, with or without the presence of a previous retinochoroiditic scar, (2) the presence of serum toxoplasma IgG and/or IgM antibodies, and (3) the exclusion of other causes of retinitis by serologic and radiologic work-up. Purified protein derivative (PPD) skin test was done to all patients and laboratory work-up was performed whenever indicated to exclude other causes of retinitis. The diagnosis was verified by at least two clinicians including a uveitis specialist.

Medical Intervention

All patients received azithromycin 500 mg orally daily with sulfamethoxazole 160 mg and trimethoprim 800 mg orally daily for a period of 4 weeks. In addition, seven patients were given prednisone 1 mg/kg/day orally 48 hours after starting the antimicrobial therapy and tapered over a period of one month. Five patients received a single injection of subtenon triamcinolone acetonide 40 mg, 48 hours after starting the antimicrobial therapy. Patients with evidence of anterior chamber cells and inflammatory reaction were treated with topical nonsteroidal anti-inflammatory drugs and/or topical prednisolone acetate depending on the grade of inflammation in the anterior chamber. The topical medications were tapered down with a corresponding decrease in inflammation in the anterior segment.

Outcome measures

Final visual acuity assessed by Snellen chart and anatomic integrity of the macula after resolution of the retinochoroiditis documented by OCT and fundus photos were the main outcome measures.

Results

There were a total of 12 patients with 8 males and 4 females. The mean age was 34 years with an age range of 16-54 years. Patients were followed up for a period of 4 to 12 months with a mean period of 6 months. Macular toxoplasmic lesions measured 1.5 mm or less and were associated with macular edema. All patients had visual acuity of 20/200 or less at presentation except for two patients who presented with a visual acuity of 20/40 and 20/120 respectively. Following treatment, all patients showed clinical improvement in inflammation, visual acuity and macular anatomic changes at 1 and 6 months follow-up. Clinical improvement in inflammation was defined as decrease in anterior chamber and vitreous cells, demarcation of the edge of lesion, decrease in retinal infiltration, decrease in adjacent vasculitis if present, and resolution of macular edema clinically and by OCT. Eight (67%) out of the twelve patients had visual acuity better than 20/60 at 1 month follow-up and nine (75%) patients had better than 20/40 visual acuity at 6 months follow-up. Ten patients (83%) had a residual macular scar (Figures 1 and 2) causing a variable degree of visual loss.

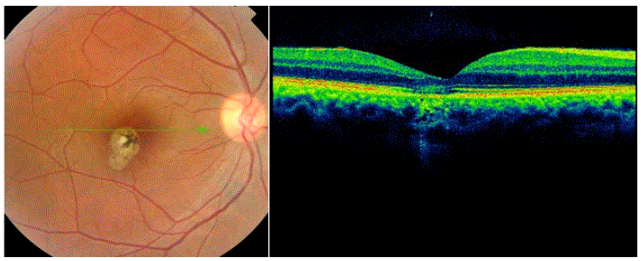

Figure 1: Fundus photo and spectral domain OCT showing toxoplasmic macular scar and loss of macular photoreceptors.

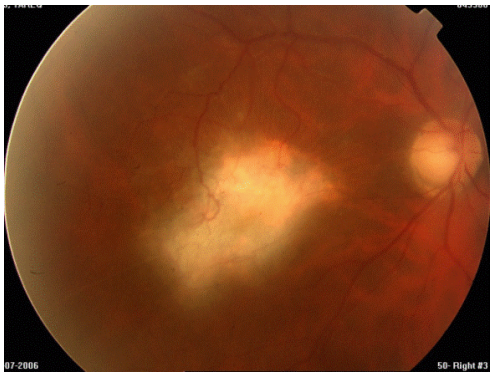

Figure 2: Fundus photo of patient 10 with delayed treatment showing a large macular scar.

Interestingly, two patients (17%) had complete resolution of the macular retinochoroiditis, macular edema and adjacent vasculitis without a residual scar and regained 20/20 and 20/16 vision respectively (Figures 3A-E and 4A-D). Both presented and were treated within the first 24 hours of symptoms' onset, whereas all other patients presented at least 6 days after their visual symptoms started (Table 1).

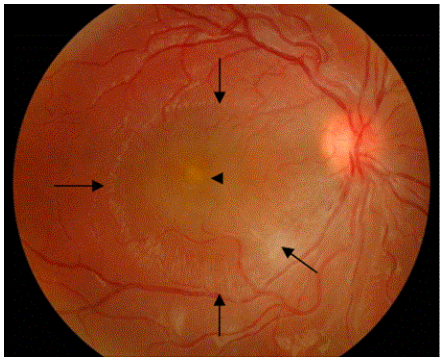

Figure 3A: Fundus photo of patient 11 showing small foveal infiltrate (arrow head) and significant macular edema (long arrows) (before treatment).

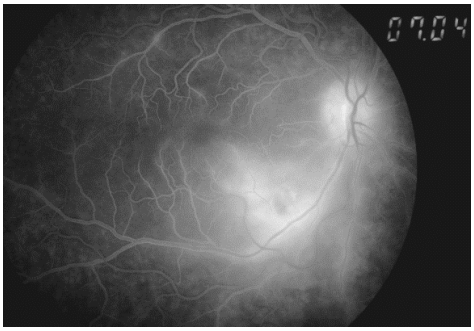

Figure 3B: Flourescein Angiography of patient 11 showing active vasculitis and leakage inferior to the optic nerve (before treatment).

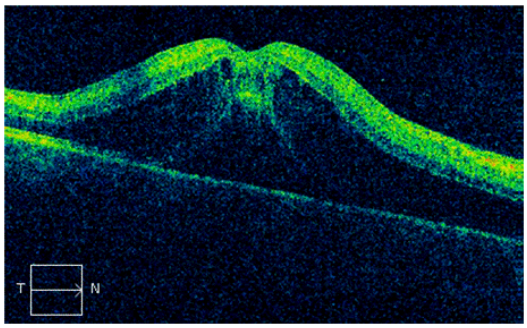

Figure 3C: Spectral Domain OCT of patient 11 showing a hyperreflective subfoveal lesion/infiltrate with serous macular detachment (before treatment).

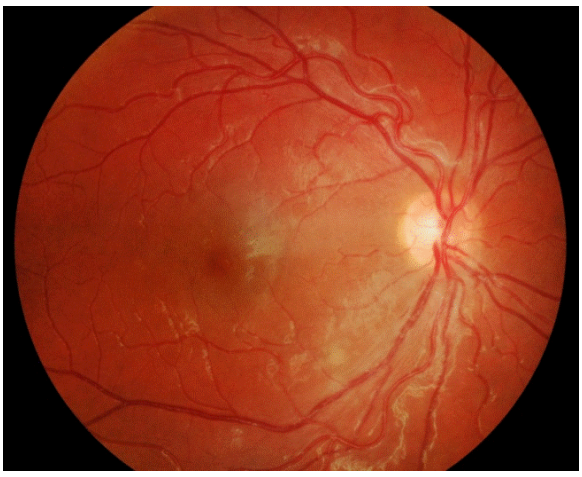

Figure 3D: Fundus photo of patient 11 showing complete resolution of foveal lesion and resolution of macular edema with no residual scarring (after treatment).

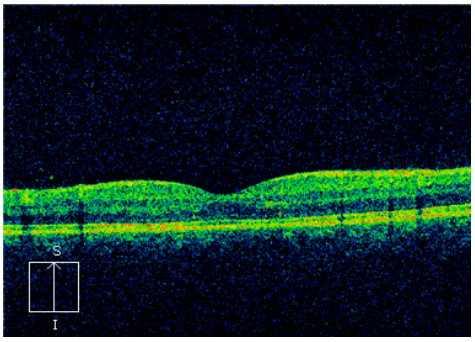

Figure 3E: Spectral Domain OCT of patient 11 showing resolution of serous macular detachment and restoration of normal macular anatomy.

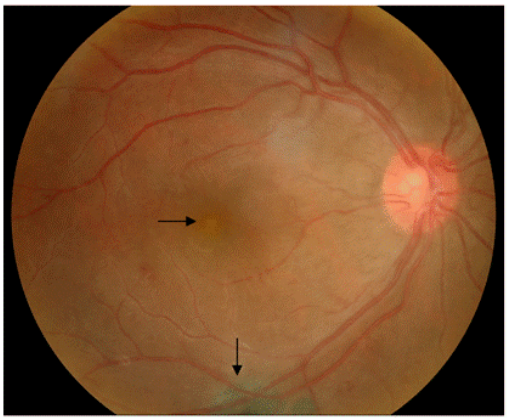

Figure 4A: Fundus photo of patient 12 showing small active foveal infiltrate (horizontal arrow) before treatment and an old inferior toxoplasmic scar (vertical arrow).

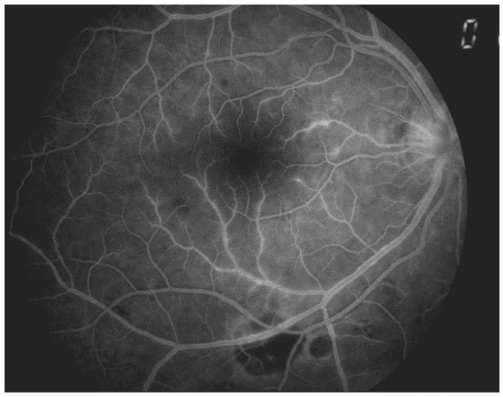

Figure 4B: Flourescein Angiography of patient 12 showing mild perimacular vasculitis.

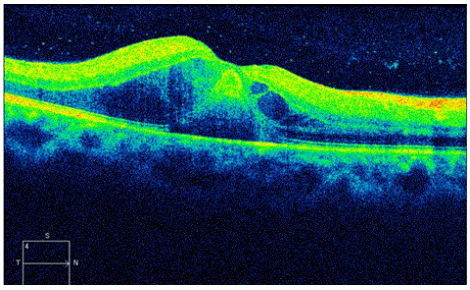

Figure 4C: Spectral Domain OCT of patient 12 showing a hyperreflective subfoveal lesion/infiltrate with serous macular detachment (before treatment).

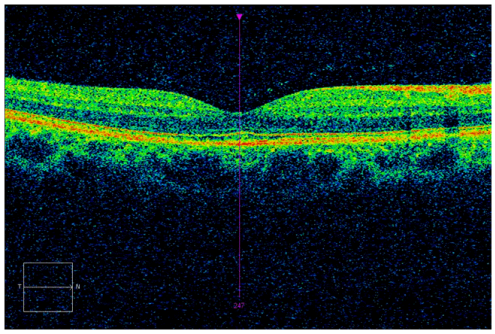

Figure 4D: Spectral Domain OCT of patient 12 showing total resolution of edema without macular scarring.

Seven (58%) out of the twelve patients had one or more healed toxoplasmic scar near the active macular lesion at presentation indicating a recurrent disease (Figure 5). IgG antibodies were positive in ten out of the twelve patients, and IgM antibodies were positive only in two patients. Only one patient developed ocular hypertension which was controlled by topical intraocular pressure-lowering agents. No other side effects were noted from the posterior retroseptal injections of 40 mg triamcinolone acetonide or systemic steroids.

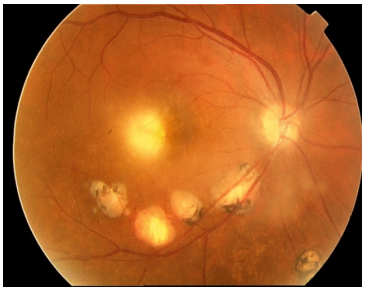

Figure 5: Fundus photo of a patient with multiple chorioretinal scars inferior to the active macular lesion.

Discussion

Ocular toxoplasmosis or toxoplasmic retinochoroiditis is one of the most frequently identifiable causes of posterior uveitis accounting for up to 50% of all cases worldwide [17]. Toxoplasmic retinochoroiditis is characterized by a localized focus of necrotizing retinitis surrounded by retinal edema with subjacent choroiditis. It can also be associated with overlying vitritis and adjacent vasculitis. The ocular lesion may be single or multiple, small or large, and may reach several disc diameters in size. Macular toxoplasmic lesions are more likely to cause marked decrease in visual acuity when compared to peripheral lesions. In immunocompetent hosts, toxoplasmic retinochoroiditis typically resolves over a period of 1 to 2 months. Despite being a self-limiting disease in most instances, Toxoplasma infection may cause decreased vision secondary to optic nerve or macular involvement, and/or severe vitreous inflammation [10].

Macular toxoplasmic retinochoroiditis may threaten the photoreceptors in the macular area and can lead to relentless destruction of the retina and choroid leading to loss of central vision. Macular retinochoroiditis is usually associated with macular edema and may lead to serous detachment despite the use of antimicrobial agents [9]. Macular lesions can significantly affect vision during the active phase which makes patients seek medical attention earlier. A residual macular scar is a main complication of macular toxoplasmic retinochoroiditis and, unlike a peripheral scar, can cause permanent loss of vision to a variable degree depending on the size and depth of the scar (Figures 1 and 2). Also, a toxoplasmic scar can be associated with considerable field loss when it occurs close to the optic nerve head [19]. Rothova et al. have shown in a study on 149 consecutive patients that treated patients showed a greater reduction in the size of the retinal lesion in comparison with the untreated group [17]. This becomes particularly important when the toxoplasmic lesion is adjacent to the optic nerve head or involves the macula.

Several studies were conducted to assess the efficacy of treatment of ocular toxoplasmosis. The use of azithromycin combined with trimethoprim and sulfamethoxazole has been found to be safe and effective compared to other antimicrobial agents [20,21]. Azithromycin has the characteristic feature of having sustained concentration in tissues with a long half-life and a relatively better safety profile [22]. A systematic review of 368 titles and abstracts was performed to assess the effects of adjunctive use of corticosteroids for ocular toxoplasmosis. Although research has identified wide variation in practices regarding use of corticosteroids, the systematic review did not identify evidence from randomized controlled trials for the role of corticosteroids in the management of ocular toxoplasmosis [11]. Nonetheless, about 82 percent of the members in an American Uveitis Society survey utilized systemic corticosteroids in the management of ocular toxoplasmosis [12]. In our patients, we found that the combination of antimicrobial therapy with steroids appears to be effective in controlling the inflammation, accelerating the resolution of macular edema and consequently preventing major damage to vision threatening structures.

All our patients showed progressive improvement in the signs and symptoms of macular retinochoroiditis within the first two weeks of starting treatment and 75% of them achieved 20/40 visual acuity or better at 6 months.

Posterior subtenon's steroid injection may be a good alternative to systemic steroids; however, it can lead to orbital abscess, ocular hypertension and steroid-induced glaucoma [14,15]. Clinical studies to prove the safety and efficacy of periocular steroid injections in macular and paramacular toxoplasmic retinochoroiditis are still needed. The combination of intravitreal clindamycin and dexamethasone was found to be associated with resolution of toxoplasmic retinochoroiditis and functional and anatomic improvement in patients who did not tolerate, had contraindications to, or did not respond to oral medications [12,13].

In our cohort of patients, we have observed that delayed treatment may more likely lead to a residual macular scar (10 out of 12 patients) and consequently worse visual outcome as compared to early treatment. Two of our patients (11 and 12, Table 1) presented with visually significant macular toxoplasmosis within the first 24 hours of symptoms onset and were treated promptly. They both had early non-necrotizing macular infiltration with significant macular edema detected clinically and by OCT. After treatment, both patients achieved complete resolution of macular infiltration, surrounding edema and adjacent vasculitis without residual scarring (Figures 3A-E, 4A-D) and regained 20/20 and 20/16 visual acuity respectively. One of the two patients (patient 12) had an old toxoplasmic scar inferior to the active lesion indicating a recurrent disease (Figure 4A) and showed clinical improvement within the first 48 hours of anti-parasitic treatment even before systemic steroids were started. On the other hand, delayed treatment and large macular infiltrates resulted in a macular scar and worse visual outcome (Figure 2).

It is still unclear what factors put a patient at higher risk of developing a residual macular scar after the retinochoroiditis resolves. In our study, one possible explanation is that early diagnosis and prompt treatment may decrease the risk of macular scarring. Early containment of the parasite and control of the acute inflammation and macular edema with anti-parasitic agents and steroids may protect the photoreceptors and reduce the risk of macular damage. Another explanation might be related to the virulence of the parasite. Variations that are observed in the severity of toxoplasmic retinochoroiditis reflect a complex interplay between the host immune defenses, parasite virulence and environmental factors [2]. The main limitation of our study is the small sample size. Larger comparative clinical studies are needed to validate our findings.

Recurrence of toxoplasmic retinitis occurred in two of our cases during the follow-up period. Recurrence risk seems to be influenced by patient age and duration of infection [18]. Long term intermittent trimethoprim and sulfamethoxazole prophylactic treatment may decrease the recurrence of toxoplasmic retinochoroiditis [18,20]. The treatment consists of the administration of sulfamethoxazole 800 mg and trimethoprim 160 mg every 3 days. It seems that all the available drugs are incapable of eradicating the latent tissue cysts; recurrences were observed with all treatment modalities [23,24].

The visual and structural outcome of macular toxoplasmosis treated with antimicrobial agents and steroids was good. Residual macular scar after the retinochoroiditis resolves was the main cause of poor visual outcome. Early diagnosis and prompt treatment of macular toxoplasmosis characterized by a small area of infiltration without necrosis may preserve vision threatening structures and consequently lead to better visual outcome. Prophylactic treatment may be considered especially in patients with retinochoroiditic scars that are close to the macula.

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