· Case report ·

Exacerbation of recurrent acquired ocular toxoplasmosis after an initial response to treatment: a case report

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Abstract

• AIM: To report unusual exacerbation of recurrent acquired ocular toxoplasmosis and improvement of visual outcome with proper treatment in an immunocompetent individual.

• METHODS: Case report.

• RESULTS: A 21-year-old Bisaya girl, otherwise healthy, with contact history with cats, presented with right eye painless and progressive blurring of vision for two weeks. The visual acuity was 6/15 in the right eye and 6/6 in the left eye. Fundus examination showed focal retinitis in the posterior pole with swollen hyperemic optic disc in the right eye and old retinochoroidal scars in the periphery of both eyes. She had right recurrent ocular toxoplasmosis that was confirmed with toxoplasma serology. Initially, she responded to two different treatments such as bactrim and azithromycin. Unfortunately, she developed two episodes of exacerbation of toxoplasmosis in right eye during the course of treatment. Her right eye visual acuity was decreased to 6/60. The medication regime consisted of oral azithromycin with tapering doses of corticosteroids was subsequently initiated in this patient for 6 weeks. The toxoplasmic retinitis in the right eye was resolved and there was no recurrence during the last 1 year follow-up. Her final visual acuity was 6/30 in right eye and 6/6 in left eye.

• CONCLUSION: Recurrent acquired ocular toxoplasmosis in an immunocompetent individual is not common. Delayed diagnosis and treatment result in permanent blindness. Prompt, adequate and compliance of treatment are essential to prevent this devastating visual complication.

• KEYWORDS: *Toxoplasma gondii*; ocular toxoplasmosis; bactrim; azithromycin; corticosteroids
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INTRODUCTION

Toxoplasmosis is a parasitic disease caused by the ubiquitous, obligate intracellular protozoan *Toxoplasma gondii*. It can be either congenital or acquired infection. It has systemic and ocular manifestations[1,2]. The clinical presentation, course and visual outcome of ocular toxoplasmosis vary with individuals and depend on the immune status of individuals as well as the location and severity of the infection. The hallmark of an active lesion of ocular toxoplasmosis in immunocompetent individuals is a focal retinochoroiditis characterized by a fresh, cream-colored elevated lesion and overlying vitritis that appears as 'headlight in the fog'. The new focal lesion adjacent to an old retinochoroidal scar manifests as 'satellite lesion'[2-4]. In some individuals, the lesion can develop far away from pre-existing scar as a new primary retinal lesion. Multiple active lesions are found in one or both eyes in immunocompromised patients. Ocular toxoplasmosis commonly affects the macula leading to severe visual impairment. Papillitis and neuroretinitis are the less common features in ocular toxoplasmosis[4]. Ocular toxoplasmosis is a self limiting disease. Recurrences occur especially in immunocompromised individuals[2]. Management of recurrent ocular toxoplasmosis with frequent exacerbation is challenging. This case illustrates unusual presentation of ocular toxoplasmosis in an immunocompetent individual and the importance of proper diagnosis and early intervention to improve visual outcome.

CASE REPORT

A 21-year-old Bisaya girl, single, presented to our clinic with complaint of painless, decreased vision in the right eye for 2 weeks. It was insidious in onset, progressively worsened and affected her central vision. It was not associated with photophobia, floaters, and redness of eyes. Premorbidly, her vision was good and equal in both eyes. There was significant history of contact with cats. She has no history of ocular trauma, tuberculosis infection and no history suggestive of immunocompromised state. Her family medical and ocular histories were unremarkable. On examination, the visual acuity was 6/15 in the right eye and 6/6 in the left eye. Her pupils were equal and reactive to light. Relative afferent pupillary defect was negative. Slit-lamp examination of anterior segment of both eyes were unremarkable. Intraocular

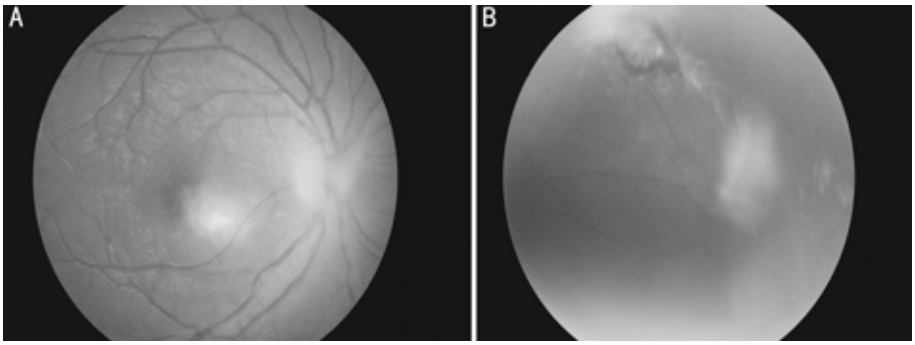

Figure 1　A: Focal fluffy creamy white retinal lesion involving macula in the right eye; B: Old peripheral retinochoroidal scar in the left eye.

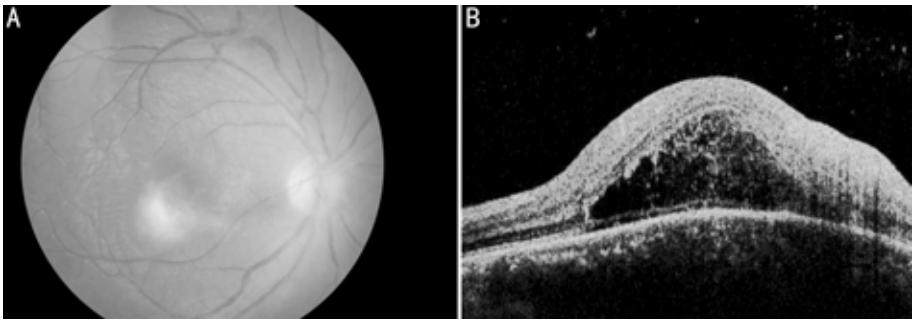

Figure 2　A: Increased fluffy creamy white retinal lesion adjacent to the initial lesion occurred 1 month after treatment of 3 days azithromycin 500mg daily with tapering doses of oral prednisolone; B:Optical coherence tomography revealed subretinal fluid accumulation.

pressure revealed 14mmHg in the right eye and 12mmHg in the left eye. Fundus examination of the right eye showed focal fluffy creamy white retinal lesion involving macula inferonasally, hyperemic optic disc swelling (Figure 1A) and an old retinochoroidal scar noted superiorly at 12 o'clock. Left fundus examination revealed two old retinochoroidal scars noted superiorly at 10 and 12 o'clock (Figure 1B). Left eye optic disc and macula were normal. There was no vitritis and vasculitis found on fundus examination. Systemic examinations were unremarkable. Her anti-toxoplasma IgG was positive but negative for anti-toxoplasma IgM. The erythrocyte sedimentation rate (ESR) was slightly elevated (18mm/h). The mantoux test was negative and chest X-ray was normal finding. The VDRL, TPHA and HIV ELISA investigations were negative. She was screened for connective tissue disorder including rheumatoid factor, C3, C4 , ANA, and dsDNA. All the results were negative. Other blood investigation such as full blood count, blood urea serum electrolytes and random blood sugar were within normal limit. The patient was diagnosed to have right recurrent acquired ocular toxoplasmosis based on clinical features and *Toxoplasma gondii* antibodies result.

She was promptly started on bactrim (400mg sulfamethoxazole/80mg trimethoprim), two tablets twice a day and planned for at least 6 weeks treatment with bactrim. She returned to the clinic in 1 week for assessment. At her visit, right eye visual acuity was improved to 6/6, the fluffy creamy white retinal lesion was decreased in size and the optic disc swelling became less. Her bactrim was continued, and she was advised to return to the clinic in 3 weeks. However, she has an exacerbation of right ocular toxoplasmosis after she stopped taking bactrim for 2 weeks because of intolerance of the side effects such as nausea and epigastric pain. The focal white retinal lesion was increased in size and the visual acuity was decreased to 6/15 in the right eye. Her left eye remained stable and visual acuity was 6/6 in the left eye. She was subsequently given 500mg azithromycin daily for 3 successive days with slow tapering doses of oral prednisolone. Oral prednisolone was started with 1mg/kg daily and tapered over 1.5 months. In addition, 150mg ranitidine was given twice daily. Initially, the right eye condition was improved after 1 week. Unfortunately, 1.5 months later, she developed another exacerbation of right ocular toxoplasmosis. Her visual acuity of right eye was decreased to 6/60 and right fundus showed mild optic disc swelling with increased size and intensity of fluffy creamy white retinal lesion adjacent to the initial lesion (Figure 2A). Optical coherence tomography revealed subretinal fluid accumulation and increased thickness of sensory retina (Figure 2B).

At that time, the medication regime was changed to 6 weeks duration with a combination of tablet azithromycin 500mg daily and tapering doses of tablet prednisolone. Oral prednisolone was started with 1mg/kg daily which was tapered slowly. Tablet ranitidine 150mg twice daily was given too. The patient was instructed to return to the clinic every week for assessment and monitoring of the response and side effects of treatment. The patient responded and tolerated to this regime of medication well. Her blood pressure, intraocular pressure and blood sugar level were normal throughout her visits.

One week after treatment, her right eye visual acuity was improved to 6/48. The creamy white retinal lesion was decreased in size and became less fluffy (Figure 3A). Weekly visits showed favourable response of treatment with improvement of the visual acuity and resolving of the right

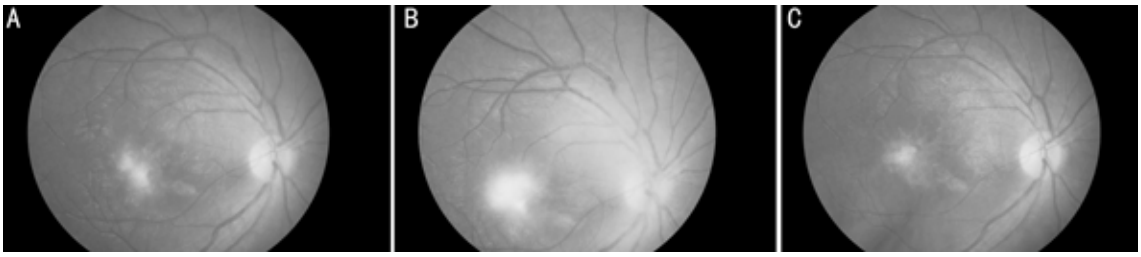

Figure 3 Right fundus: a combination treatment of azithromycin 500mg/d and tapering doses of prednisolone for 6 weeeks
A: Creamy white retinal lesion decreased after 1 week; B: Intense inflammatory reaction of retina on week-2; C: Retinal lesion resolved with scar formation after 6 weeks of treatment.

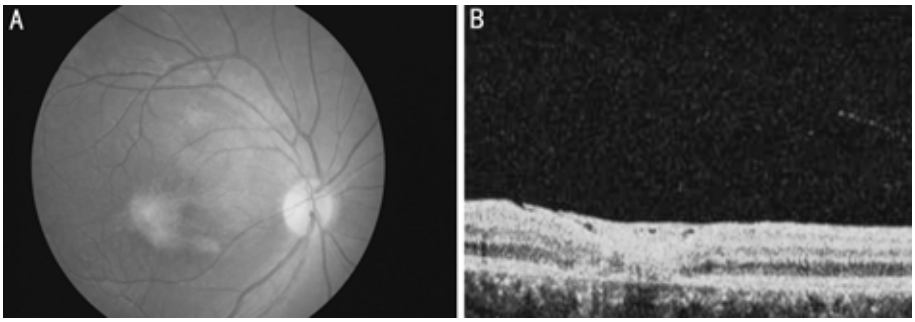

Figure 4 A: Post-treatment third month showed epiretinal membrane formation over macula; B: Optical coherence tomography revealed distortion of the macula and resolved subretinal fluid.

toxoplasmic retinal lesion. On week-2 of treatment , there was intense inflammatory reaction of the focal retinal lesion (Figure 3B). All her medication were continued and she was advised to return to clinic in 1 week. The inflammation and fluffy border of the retinal lesion gradually resolved in 1 month. After 6 weeks of treatment, the optic disc swelling subsided and the retinal lesion resolved with scar formation (Figure 3C). Post-treatment, the patient was followed up monthly. The retinal lesion continued to scar and the epiretinal membrane was formed over the macula (Figure 4A). The visual acuity of right eye was improved to 6/36. Repeated optical coherence tomography of right eye revealed distortion of macula and resolved subretinal fluid (Figure 4B). She was followed up for 1 year and there was no recurrence of ocular toxoplasmosis in the right eye. Throughout her visits, her left eye remained stable. Her final visual acuity was 6/30 in the right eye and 6/6 in the left eye.

DISCUSSION

Toxoplasma gondii is estimated to infect one-third of the human's population. Cats are the definitive host and humans are the intermediate host[1]. The cat can shed environmentally resistant eggs called oocysts. Mammals such as cow, lamb and chicken ingested vegetables that were contaminated with oocysts of cat feces. The tissue cysts of the animals contain bradyzoites. In humans, acquired infection is commonly from ingestion of undercooked meat or unwashed vegetables and fruits. Once infected, the replicating form of the parasite in the blood, namely tachyzoite may be passed across the placenta from a pregnant mother to her fetus resulting in a congenital toxoplasmosis. Toxoplasmosis can be transmitted through organ transplantation and blood transfusion[1,2].

The prevalence of *Toxoplasma gondii* infection varies in different parts of the world. In United States, the population that has been infected is 22.5% and it is estimated that 2% of the population has had episodes of ocular toxoplasmosis. Prevalence of ocular toxoplasmosis is greater in Southern Brazil[2]. Age is a risk factor of acquired infection of toxoplasmosis. The risk of infection increases with age[5]. However, ocular toxoplasmosis is commonly seen in young people and both sexes are equally affected by the disease[4]. The common clinical presentation of ocular toxoplasmosis is retinochoroiditis. The primary toxoplasmic lesion begins in the superficial layers of the retina. The retinitis is due to the rapid replication of tachyzoites within retina together with the immune response to this pathogen. Subsequently, this cascade of inflammation involves the retina pigment epithelium and choroid resulting in choroiditis. Tachyzoites can differentiate into latent bradyzoites in the retina as tissue cysts[1,4].

Recurrences can occur in congenital and acquired ocular toxoplasmosis. It is attributable to reactivation of these parasites or reinfection of the host. Reactivation results in the release of these parasites from tissue cysts in the retina or the dissemination of parasites from non-ocular sites to the eye of the host. Risk of recurrences are increased with age, immunosuppression and pregnancy. The exact mechanism that contributes to reactivation of these parasites remains uncertain. It is postulated that it could be as a result of hormonal or immunological changes of the host[2,6,7].

Clinical presentation of ocular toxoplasmosis depends on the location and severity of the infection in the eye. Retinochoroiditis is a common presentation in ocular toxoplasmosis. There are various etiologies of retinochoroiditis besides ocular toxoplasmosis such as cytomegalovirus retinitis, tuberculosis, syphilis, and ocular histoplasmosis.

Retinochoroiditis with overlying vitritis and near to an old retinochoroidal scar is a classic presentation in ocular toxoplasmosis[3]. Sometimes, this lesion can develop far away from pre-existing scar as a new primary retinal lesion. This primary new retinal lesion can be due to reactivation of the parasites or reinfection of the host[2]. There are atypical presentation in ocular toxoplasmosis such as papillitis, neuroretinitis, retrobulbar neuritis, choroidal neovascularisation, vasculitis, serous retinal detachment and scleritis[8,9]. The toxoplasmic retinochoroidal lesion is frequently located at the macula. Atmaca *et al*[4] conducted a study of ocular toxoplasmosis in 189 patients from 1972 to 1999 at eye clinic of Ankara University Medical School and at private clinic of Dr Atmaca. They found the lesions were located at the macula in 59% of the eyes whereas at the macula and peripheral retina in 25% of the eyes. Bilateral macula lesions are more common in the congenital ocular toxoplasmosis. It can be associated with systemic manifestation such as cranial calcifications, hydrocephalus, and convulsions.

Our patient has focal retinitis in the right eye and peripheral old retinochoroidal scars in both eyes. The active focal lesion in the macula was far from peripheral retinochoroidal scars and the lesion was associated with optic disc swelling but no overlying vitritis seen. This clinical findings are not the classic presentation of retinochoroiditis of ocular toxoplasmosis. Therefore, other infective and connective tissue diseases work up are mandatory in this case. She was asymptomatic in early age because the toxoplasmic retinochoroiditis lesions were located at the peripheral retina. The course of toxoplasmic retinochoroiditis is self limiting. Small peripheral retina lesions heal spontaneously with pigmented border scar formation. Recurrences can be due to reinfection of *Toxoplasma gondii* or reactivation of these parasite from the tissue cyst in the retina. Risk factors of recurrences are age, immunosuppression and pregnancy. The risk factors of her recurrence remains unknown. Probably, it was due to reinfection of *Toxoplasma gondii* because she had history of contact with her cats.

Toxoplasma serology is a supportive measurement of diagnosis. First immunoglobulin to appear in the immune response is immunoglobulin M (IgM). Immunoglobulin G (IgG) is the predominant antibody that appears in the secondary immune response, commonly seen in recurrent exposure to an antigen. Serum anti-toxoplasma IgM is positive in recent infection in ocular toxoplasmosis. Later, the serum anti-toxoplasma IgG will appear. However, absence of serum anti-toxoplasma IgM and IgG do not exclude the diagnosis of ocular toxoplasmosis. Ongkosuwito *et al*[10] conducted a study of toxoplasma serology in 22 patients with primary ocular toxoplasmosis and 42 patients with recurrent ocular toxoplasmosis. Primary ocular toxoplasmosis is the primary lesion that is not from the scar. They found serum anti-toxoplasma IgG(above level 1:4096) and anti-toxoplasma IgM were absent in patients with recurrent ocular toxoplasmosis. Serum anti-toxoplasma IgG (below level 1:512) was present in 62% of patients with recurrent ocular toxoplasmosis and 14% of patients with primary ocular toxoplasmosis. Serum anti-toxoplasma IgM was present in 6 patients with primary ocular toxoplasmosis but absent in patients with recurrent ocular toxoplasmosis[10].

The need of treatment depends on the location of lesion and the severity of the inflammation. Small peripheral retinal lesion heals spontaneously without treatment. Treatment is needed for sight-threatening lesion at the macula and optic disc. It should be started promptly in order to prevent severe visual impairment. There are various treatment of ocular toxoplasmosis such as pyrimethamine, sulfadiazine, clindamycin, trimethoprim, sulfamethoxazole, azithromycin, spiramycin or a combination of these drugs.

The classic treatment of ocular toxoplasmosis is the combination of pyrimethamine, sulfadiazine and prednisolone. Bactrim consists of the combination of trimethoprim and sulfamethoxazole. Soheilian *et al*[11] conducted a controlled, randomized, single-blind study of comparison between bactrim and classic treatment in the ocular toxoplasmosis at Labbafinejad Medical Center Uveitis Clinic in Tehran, Iran from January 2000 to February 2004. A total of 59 patients were recruited in this study. 29 patients were treated with classic treatment and 30 patients were treated with bactrim. They found no difference in efficacy between these two groups of treatment. Retinochoroiditis resolved in all patients over 6 weeks treatment[11]. We started bactrim for our patient. It showed good response initially. The first exacerbation of ocular toxoplasmosis occurred because the poor compliance with medication. The patient stopped bactrim herself because of the intolerance of side effects.

Azithromycin was subsequently given to the patient. Azithromycin is an effective alternative treatment and it penetrates blood-brain and blood-ocular barriers. Rothova *et al*[12] conducted a study of azithromycin in 11 immunocompetent patients with ocular toxoplasmosis. They found 7 patients had good response including two patients with progressive retinitis despite previous classic treatment[12]. Prednisolone was given together with azithromycin in our patient because of the severe inflammation that involved the macula. The second episode of exacerbation of ocular toxoplasmosis in our patient was due to short duration of azithromycin treatment. After the second episode of exacerbation in our patient, there was severe inflammation of the retina and increased size of the focal lesion in the right eye macula resulting in severe visual impairment.

Rothova *et al*[13] conducted a prospective multicenter study of therapy in 106 patients with active toxoplasmic retinochoroiditis at 5 hospitals in the Netherlands. They found that the most important predicting factor of the duration of inflammatory activity was the size of the retinal focus lesion. The large retinal lesions were associated with longer duration of inflammation and recovery time[13]. Therefore, a 6-week course of azithromycin together with prednisolone were promptly given. Our patient responded well to this regime. We found the active toxoplasmic lesion was resolved after 6

weeks treatment. The visual outcome was improved. She has no recurrence during follow-up period. In conclusion, it is essential for ophthalmologists to be aware of the severity of exacerbation of recurrent ocular toxoplasmosis. Early diagnosis, compliance and longer duration of treatment are important in this condition in order to obtain good outcome.

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免疫功能正常的复发性后天性眼弓形体病1例

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摘要

目的:报告1例免疫功能正常的患者患复发性后天性眼弓形体病的异常恶化及治疗后视力的改善。

方法:病例报告。

结果:比沙亚族女孩,21岁,其它方面健康,有与猫接触史,表现为右眼无痛、渐进性视力模糊2wk。视力右眼6/15,左眼6/6。眼底检查呈右眼后极部局灶性视网膜炎,伴视盘肿胀充血,双眼周边陈旧性视网膜脉络膜疤痕。经弓形虫血清检查证实其右眼患复发性眼弓形虫病。起初,患者对复方新诺明和阿奇霉素两种药物反应良好。然而在治疗过程中患者右眼弓形体病两次恶化,右眼视力下降到6/60,随后进行持续6wk的口服阿奇霉素和逐渐减量的皮质类固醇药物治疗,右眼弓形虫性视网膜炎治愈,随访1a未见复发。患者最终视力,右眼6/30,左眼6/ 6。

结论:患复发性后天性眼弓形体病在免疫功能正常的个体并不常见。延误诊断和治疗导致永久性失明。及时、充分的治疗和良好的治疗依从性对防止并发症毁坏视觉极其重要。

关键词:弓形虫;眼弓形虫病;复方新诺明;阿奇霉素;皮质类固醇