CHALLENGES OF OCULAR TOXOPLASMOSIS TREATMENT IN MULTIPLE DRUG INTOLERANCE SYNDROME: A CASE REPORT AND LITERATURE REVIEW

Kaur R[1], Iqbal T[1], Juana A[1], and Lott PW[1].
[1]University Malaya Eye Research Centre, Department of Ophthalmology, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia

Correspondence:
Penny Pooi Wah Lott,
University Malaya Eye Research Centre,
Department of Ophthalmology,
Faculty of Medicine,
Universiti Malaya,
50603 Kuala Lumpur, Malaysia
Email: lottpw@yahoo.com

Abstract

We report a literature review and a case of ocular toxoplasmosis in a patient with multiple drug allergies, who was successfully treated with regular intravitreal clindamycin and subconjunctival dexamethasone. A Malay lady in her twenties presented to us with right eye blurring of vision of 2 weeks duration, which she described as a central scotoma. Visual acuity at presentation was hand movements. Examination revealed intense ocular inflammation. The right eye had anterior segment inflammation of 3+ cells with fine keratic precipitates, whilst the posterior segment revealed papillitis, vitritis, retinitis, choroiditis, vasculitis and hyperpigmented chorioretinal scar inferotemporal to fovea. Ocular coherence tomography showed intraretinal fluid and retinal thickening. Fluorescein angiography showed early hypofluorescence of the lesion with progressive hyperfluorescence and leakage from the optic disc. Immunoglobulin G serology of *Toxoplasma gondii* was raised and immunoglobulin M levels were normal. The patient developed an allergic reaction with classical antibiotic and antifolate therapy. She was successfully treated with regular two-weekly intravitreal clindamycin and subconjunctival dexamethasone and her best corrected visual acuity was 6/18 at the end of her treatment. Intravitreal injection of clindamycin and subconjunctival dexamethasone is a good option in patients of ocular toxoplasmosis who are allergic to oral medications.

Keywords: Ocular Toxoplasmosis, Anti-folates, Macrolide Antibiotics, Allergic Reaction, Intravitreal Clindamycin

Introduction

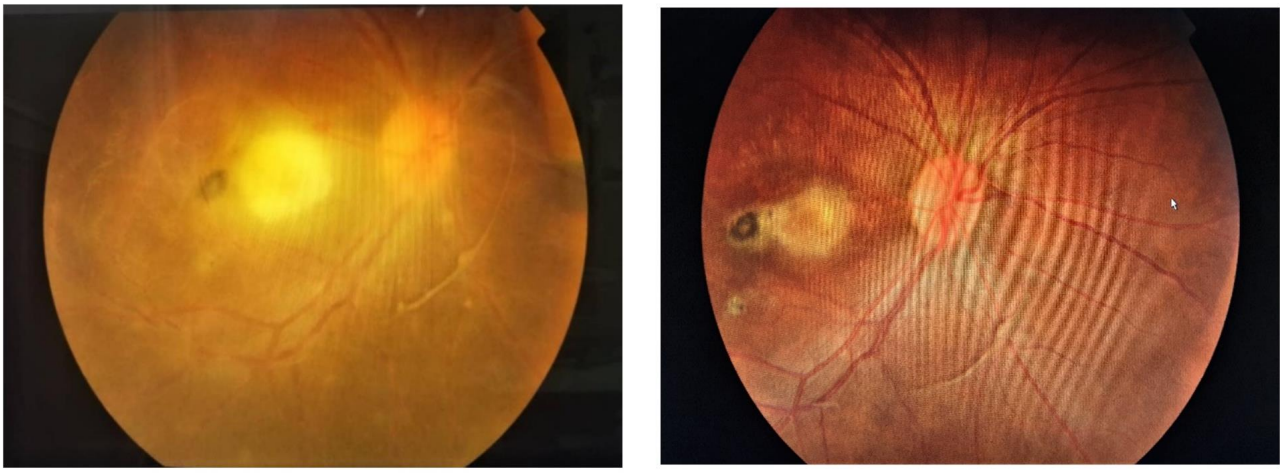
Toxoplasma gondii is an intracellular protozoan that is the leading infectious cause of posterior uveitis (1, 2). In some countries, up to half of the cases presenting with posterior uveitis can be attributed to this organism (3, 4). Toxoplasmosis is common in Malaysia; nevertheless, little studies have been conducted on ocular toxoplasmosis in this country (5). Ocular toxoplasmosis may result in significant morbidity and vision loss especially if there is a delay in diagnosis and treatment (1, 6). The diagnosis of ocular toxoplasmosis depends mainly on the presence of typical lesions, with retinochoroiditis being the key clinical feature and frequently involving the posterior pole. Resolution of active lesions results in hyperpigmented chorioretinal scars (7-9). We report a case of recurrent full blown ocular toxoplasmosis in a patient having adverse reaction to two classes of drugs, which included anti-folates (trimetroprim-sulfamethaxazole; TMP-SMX) and macrolide antibiotics (azithromycin and erythromycin). The patient was successfully treated with frequent and regular two-weekly intravitreal clindamycin and subconjunctival dexamethasone. The literature is reviewed in brief.

Case Report

A 22-year-old Malay lady presented to us with right eye blurring of vision of two weeks duration, which she described as a central scotoma. She also experienced seeing multiple black spots or floaters but there was no redness or photophobia. She did not have symptoms of sore throat, fever, body ache or maculopapular rash prior to the onset of eye symptoms. Her medical history was unremarkable except for a few episodes of minor drug allergy to non-steroidal anti-inflammatory agents. She denied having any pets at home.

On examination, her right eye vision was hand movement (HM) and left eye was 6/6. There was grade 3 right relative afferent pupillary defect. Intraocular pressure

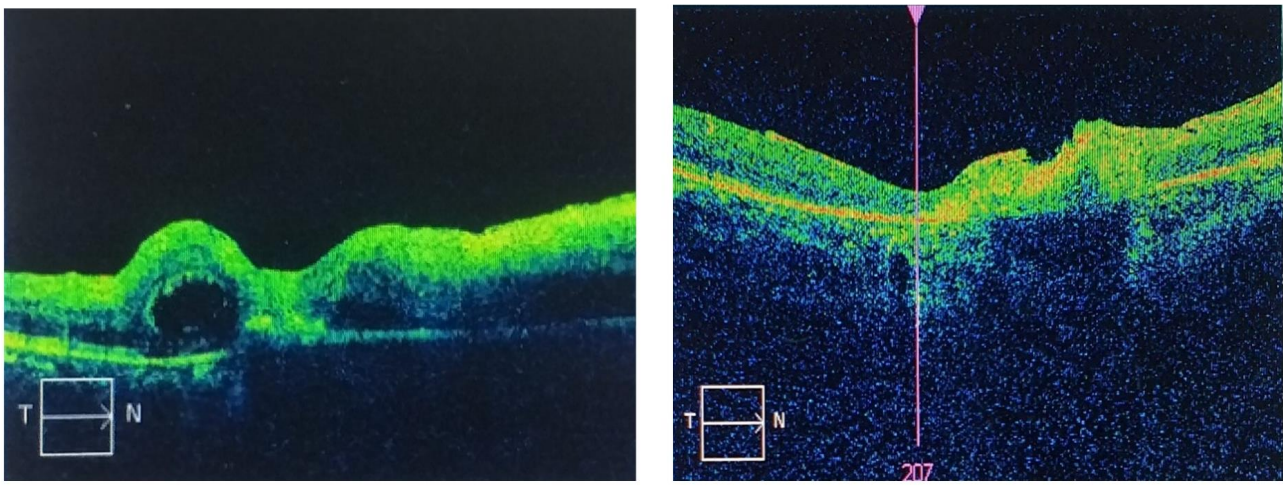
was within normal range for both eyes. The right eye had anterior segment inflammation of 3+ cells with fine keratic precipitates on the inferior cornea. There was also vitritis and the optic disc was swollen. There was an area of hyperpigmented chorioretinal scar inferotemporal to fovea with adjacent retinitis (Figure 1a). There was also choroiditis at the superior and temporal retina, with vascular sheathing, circumferential vasculitis and chorioretinitis along the vessels. Left eye was unremarkable. Systemically, patient had no cervical lymphadenopathy or arthralgia on presentation.



(a) (b)

Figure 1: Fundus photo images of the right eye (a) Presenting fundus: Hyperpigmented chorioretinal scar inferotemporal to fovea with adjacent retinitis. (b) After 4th injection: Marked improvement with reduced inflammation and contracting retinitis

Spectral Domain Optical Coherence Tomography (SD-OCT) in the right eye showed intraretinal fluid and retinal thickening with central subfield thickness of 443 µm (Figure 2a). Fluorescein angiography (FFA) showed early hypofluorescence of the lesion with progressive hyperfluorescence indicating staining (Figure 3a) and leakage from the optic disc and involved vessels indicating vasculitis (Figure 3b). A serologic search for *T. gondii* infection was positive for immunoglobulin (Ig) G whereas IgM levels were normal, indicating prior exposure. White cell count, erythrocyte sedimentation rate, and c-reactive protein were in the normal range. A few other tests which included syphilis screen, tuberculosis, leptospirosis, bartonella and autoimmune screen were negative.



(a) (b)

Figure 2: Optical Coherence Tomography (OCT) images. (a) At presentation: intraretinal fluid and retinal thickening with central subfield thickness of 443 µm. (b) After 3rd injection: resolution of macula edema with subretinal fibrosis

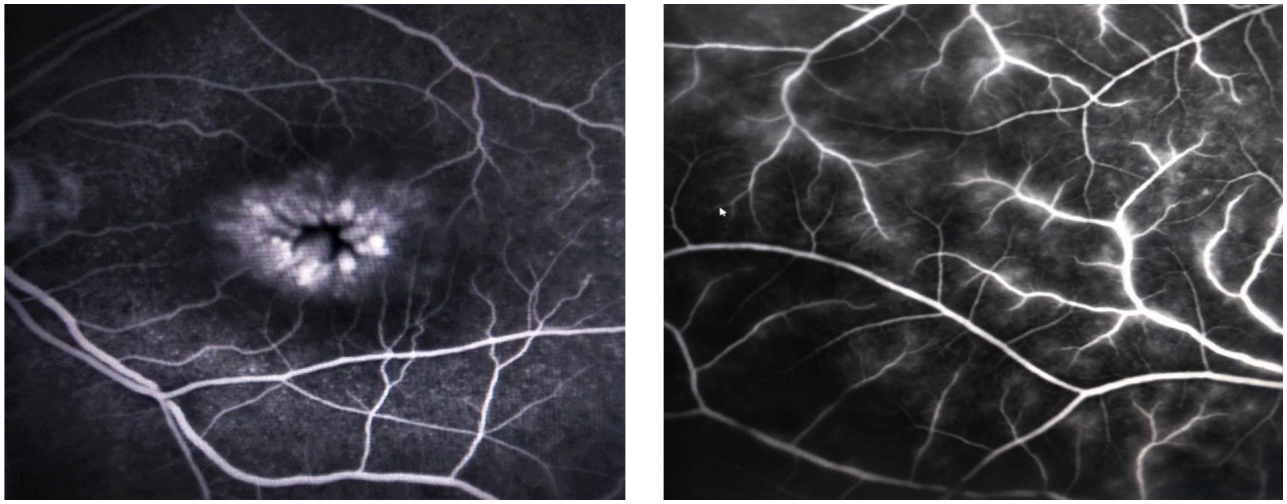


Figure 3: Fluorescein angiography (FFA) images. (a) Staining of the scar. (b) Vasculitis

The patient was treated with oral TMP-SMX 80-400 mg, two tablets daily. Once the tuberculosis screen was negative, the patient was started concurrently on oral prednisolone, 0.5 mg/kg/day. Three days after commencing treatment, the patient developed a generalized body rash, fever and palpable cervical lymph nodes. There was also a sudden drop in right eye vision to perception of light (PL) as the intraocular pressure over the right eye increased to 38 mmHg. Oral prednisolone was then increased to 1 mg/kg/day and the patient was started on topical prednisolone forte 1% 4-hourly with topical anti-glaucoma eyedrops treatment to reduce the intraocular pressure in the right eye. However, the patient developed a worsening of the generalized body rash despite the intraocular pressure in the right eye returning to normal and the significant reduction of anterior segment inflammation. The topical antiglaucoma eyedrops were discontinued and oral prednisolone was reduced to 0.5 mg/kg/day. The patient was seen again in a week and the body rash was still persistent. We decided to withhold all oral medications in view of non-resolving allergic reaction. Rashes subsequently improved. As the ocular toxoplasmosis lesions still appeared active, the patient was given a trial of oral azithromycin, 500 mg once daily dose, and oral erythromycin 400 mg twice a day, on separate occasions. However, she too developed similar allergic reactions to both medications.

Oral medications were then discontinued, and the affected right eye was treated with intravitreal clindamycin 1.5 mg/0.1 ml and subconjunctival dexamethasone 4 mg/ml injections to the eye. Three weeks after the first injection, the skin rashes resolved and vision improved to counting fingers (CF). She was given another three doses of intravitreal clindamycin 1.5 mg/0.1 ml and subconjunctival dexamethasone 4 mg/ml over a period of two months. Ocular examination noted a marked improvement with reduced inflammation and retinitis with each injection given (Figure 1b). Visual acuity continued to improve to pin-hole 6/36 and subsequently to 6/18. SD-OCT macula showed resolution of macula edema with subretinal fibrosis after 3rd injection of intravitreal clindamycin and subconjunctival dexamethasone (Figure 2b). The patient received a total of four injections of intravitreal clindamycin, 1.5 mg/0.1 ml and subconjunctival dexamethasone, 4 mg/ml.

Discussion

Ocular toxoplasmosis is caused by the protozoal organism *T. gondii*, an obligatory parasite of the cat, which then utilizes other livestock animals and humans as its intermediate hosts (10, 11). *T. gondii* infects up to a third of the world's population (12) and is common in Malaysia, with the highest prevalence in Malays as they like rearing cats as pets (5). The patient in this case, who is also a Malay, denied rearing or having contact with cats. Toxoplasmosis can also be acquired from ingesting undercooked meat, drinking water or consuming food contaminated with oocysts (10). This is the assumed route of infection in this case, as the patient eats meat and may have contracted it from contaminated or undercooked food. This patient is from Kuala Lumpur, which is an urban region, and has been reported to have a higher prevalence of toxoplasmosis (13). This is, however, contradictory to a study which reported a higher prevalence in rural as compared with suburban areas (14).

Ocular toxoplasmosis can present in one of the three phases, i.e., the active phase, chronic phase or recurrent phase (15, 16). Chorioretinitis manifests as a circular yellowish-white lesion with elevated, fuzzy margins and surrounding retinal oedema during the active phase (15, 17). The lesions are commonly seen in the macular area, as seen in this case, probably resulting from the entrapment of free parasites in capillary peri-foveal retinal terminals (15, 16). Subsequently, a well-defined hyperpigmented chorioretinal scar appears (16-18). A recurring episode is possible, particularly if the patient's immune system is impaired. Some studies have reported the incidence of recurrences being common between the first and

third decade of life (16-19). The findings in this case are consistent with these aforementioned studies (16-19), as the patient, who was also in her third decade of life, presented with a chorioretinal scar and adjacent retinitis suggesting the recurrence of active disease. This is also supported by the serology of raised IgG titres but with normal IgM titres, which suggests a previous infection rather than a recent infection.

The patient described herein was a challenge to treat as she developed adverse reactions in the form of allergic skin rash to multiple classes of drugs, including anti-folates (TMP-SMX) and macrolide antibiotics (azithromycin and erythromycin), and was also presumed to have an allergy to oral steroids as her rash worsened when oral steroid dosage was increased. These classes of drugs mentioned are the classical and alternative regimens for ocular toxoplasmosis practised by most institutions (2, 12-13, 20). We then resorted to regular 2-weekly intravitreal 1.5 mg/0.1 ml clindamycin and 4mg/ml of subconjunctival dexamethasone, as this form bypasses the ocular barriers, reduces systemic side effects and can deliver a high concentration of the drug to ocular tissues (21-24). Soheilian et al. (25) reported that treatment with 1 mg/0.1 ml intravitreal clindamycin and 400mg/0.1ml of dexamethasone had no significant outcome difference as compared to classic therapy and reported as having fewer side effects. Having a good intracellular penetration, clindamycin provides a high intracellular concentration for this intracellular parasite as it has an intracellular-to-extracellular ratio of 43 compared to other antibiotics, such as erythromycin (only 14) (25-27). The indication of intraocular therapy in toxoplasmic chorioretinitis includes contraindication to oral medications in cases of pregnancy, allergy and intolerance, unresponsiveness and lesions located at or near the optic disc and fovea (22, 28).

We did a literature review of similar reported cases of adverse effects to ocular toxoplasmosis treatment. A PubMed (National Library of Medicine) search was conducted using the two key phrases, 'intravitreal clindamycin in ocular toxoplasmosis' and 'adverse effects of toxoplasmosis treatment'.

The first search concentrated on publications which adopted intravitreal clindamycin as their first line of treatment. We found seven papers reporting on outcomes of intravitreal clindamycin as a primary treatment of ocular toxoplasmosis. These studies used various combinations of endpoints to determine the efficacy and safety of the medication. Table 1 summarizes the average injections required, time frame for improvement and adverse effects for each study conducted. All patients treated with intravitreal clindamycin did not report any adverse reactions to intravitreal clindamycin (22, 25, 28, 30-33).

Table 1: Treatment outcome of intravitreal clindamycin in ocular toxoplasmosis reported in the literature

No.	Author	Journal/Year	Country of Origin	Study Title	Results		
					Average injections	Adverse Reaction	Outcome measure
1.	Zamora et al. (30)	Arq Bras Oftalmol, 2015	Sao Paulo, Brazil	Local treatment of toxoplasmic retinochoroiditis with intravitreal clindamycin and dexamethasone	1.25	Nil	Control of TRC 100% in mean interval of 2.48 ± 1.03 weeks (2-6 weeks).
2.	Hosseini et al. (31)	Iran Red Crescent Med J, 2014	Tehran, Iran	Intravitreal clindamycin in the treatment of unresponsive zone one toxoplasmic chorioretinitis: a case report	1	Nil	Improvement in VA seen at 1 week 20/60 to 20/20 in 6 weeks
3.	Baharivand et al. (32)	Int Ophtalmol, 2012	Tabriz, Iran	Intravitreal clindamycin plus dexamethasone versus classic oral therapy in toxoplasmic retinochoroiditis: a prospective randomized clinical trial	1.13	Nil	Data compared VA and TRC at baseline and at 6 months (similar between both groups)
4.	Soheilian et al. (25)	Ophthalmology, 2011	Tehran, Iran	Randomized trial of intravitreal clindamycin and dexamethasone versus pyrimethamine, sulfadiazine, and prednisolone in treatment of ocular toxoplasmosis	1.6	Nil	Data compared VA and TRC at baseline and at 6 weeks (similar between both groups)

Table 1: Treatment outcome of intravitreal clindamycin in ocular toxoplasmosis reported in the literature (continued)

No.	Author	Journal/Year	Country of Origin	Study Title	Results		
					Average injections	Adverse Reaction	Outcome measure
5.	Lasave et al. (28)	Ophthalmology, 2010	Valencia, Spain	Intravitreal clindamycin and dexamethasone for zone 1 toxoplasmic retinochoroiditis at twenty-four months	3.6	Nil	100% patients BCVA and CMT improved and maintained for 24 months
6.	Sobrin et al. (22)	Retina, 2007	Massachusetts, USA	Intravitreal clindamycin for toxoplasmic retinochoroiditis (patients were treated with oral medication before and because of either disease progression/intolerance , given one ivt clindamycin injection)	1.17	Nil	Resolution inflammation in 83% after 1 injection in 6 weeks; Resolution of TRC in average of 1.09 months
7.	Kishore et al. (33)	Ophthalmic Surg Lasers, 2001	New Orleans, USA	Intravitreal clindamycin and dexamethasone for toxoplasmic retinochoroiditis	2-4	Nil	Control of TRC and improvement in VA 2 weeks

BCVA = Best corrected visual acuity; CMT= Central macular thickness; TRC = Toxoplasmic retinochoroiditis; VA = Visual acuity

In the second search, we focused on publications which reported adverse reactions in the classical treatment of toxoplasmosis. Therapies varied in their dosages, duration, frequency, and combinations. In our second search, we found 16 papers reporting the adverse effects and the types of reactions seen in patients. The percentage of adverse effects and the types of reactions reported are summarised in Table 2. The classical treatment of toxoplasmosis with anti-folates leads to multiple adverse effects, including gastrointestinal symptoms, hypersensitivity reactions, skin rash, elevated liver enzymes, haematological disorders, and neurological symptoms (34-49).

Table 2: Summary of adverse effects of classical treatment of toxoplasmosis reported in the literature.

No.	Author	Journal, Year	Country of Origin	Study Title	Adverse reactions (AR)	
					Treatment group = % AR	AR
1	Casoy et al. (34)	Ocul Immunol Inflamm, 2020	Sao Paulo, Brazil	Effectiveness of treatments for ocular toxoplasmosis	a) TMP + SMX = 9/236 (3.8%) b) PYR + SDZ = 9/126 (7.1%) c) Initially treated with PYR + SDZ and continued treatment with TMP + SMX and vice versa = 10/38 (26.3%) d) TMP + SMX + at least one other medication excluding PYR + SDZ = 11/26 (42.3%) e) PYR + SDZ + folinic acid = 3/12 (25%) f) PYR + SDZ + at least one other metication excluding TMP + SMX = 23 (66%) Overall = 45/451 (10%)	Maculopapular rash, n = 18 (4%) Elevated transaminase, n = 2 (0.4%) Thrombocytopenia, n = 2 (0.4%) Stevens-Johnson syndrome, n = 1 (0.2%) Lymphopenia, n = 1 (0.2%) Others, n = 21 (4.6%)

Table 2: Summary of adverse effects of classical treatment of toxoplasmosis reported in the literature. (continued)

No.	Author	Journal, Year	Country of Origin	Study Title	Adverse reactions (AR)	
					Treatment group = % AR	AR
2	Borkowski et al. (35)	Adv Exp Med Biol, 2018	Warsaw, Poland	Adverse reactions in antifolate-treated toxoplasmic retinochoroiditis	PYR + SDX + Spiramycin + Azithromycin + oral Prednisone = 213/637 (33.4%)	Elevated transaminase, n = 157 (24.6%) Thrombocytopenia, n = 53 (8.3%) Hypersensitivity reaction, n = 19 (3.0%) Gastrointestinal symptoms, n = 9 (1.4%)
3	Guaraldo et al. (36)	Trans R Soc Trop Med Hyg, 2018	Rio de Janeiro, Brazil	Ocular toxoplasmosis: adverse reactions to treatment in a Brazilian cohort	PYR + SDZ + oral Prednisone = 125/147 (85%)	Gastrointestinal Skin reactions Neurological symptoms Haematological Others
4	Lashay et al. (37)	J Curr Ophthalmol, 2017	Tehran, Iran	A prospective randomized trial of azithromycin versus trimethoprim/ sulfamethoxazole in treatment of toxoplasmic retinochoroiditis	a) Group 1 Azithromycin = 4/14 (28.5) b) Group 2 TMP + SMZ = 3/13 (23%)	a) Group 1 Mild diarrhea, n = 2 (14.2%) Skin irritation, n = 1 (7.1%) Increased serum bilirubin, n = 1 (7.1%) b) Group 2 Skin reaction, n = 3 (23%)
5	Helfenstein et al. (38)	Klin Monbl Augenheilkd, 2017	Zurich, Switzerland	Ocular toxoplasmosis: therapy-related adverse drug reactions and their management	PYR + SDZ + oral Corticosteroids = 9/49 (18.4%)	Nausea/vomiting, n = 2 (5.4%) Elevated creatinine, n = 2 (5.4%) Elevated liver enzymes, n = 2 (5.4%) Rash, n = 2 (5.4%) Facial swelling, n = 1 (2.7%)
6	Carellos et al. (39)	Pediatr Infect Dis J, 2017	Brazil	High frequency of bone marrow depression during congenital toxoplasmosis therapy in a cohort of children identified by neonatal screening in Minas Gerais, Brazil	PYR + SDZ = 75/171 (44%)	Neutropenia, n = 65 (37%) Anemia, n = 12 (16.4%) Thrombocytopenia, n = 5 (7%) Multiple blood disorder, n = 7 (9.4%) Discontinue treatment, n = 1 (1.8%)
7	Teil et al. (40)	Pediatr Infect Dis J, 2016	Lyon, France	Treatment of congenital toxoplasmosis: safety of the sulfadoxine-pyrimethamine combination in children based on a method of causality assessment	a) Group 1 PYR + SDZ = 16/65 (24.6%) b) Group 2 PYR + SDX = 37/65 (36.9%)	Neutropenia, n = 21 (32.3%) Eosinophilia, n = 17 (26.2%) Anemia, n = 14 (21.5%) Nausea/vomiting, n = 7 (10.8%) Thrombocytopenia, n = 5 (7.7%) Diarrhea, n = 4 (6.2%) Agitation, n = 4 (6.2%) Erythema, n = 1 (1.5%) Discontinue treatment, n = 7 (10.8%)

Table 2: Summary of adverse effects of classical treatment of toxoplasmosis reported in the literature. (continued)

No.	Author	Journal, Year	Country of Origin	Study Title	Adverse reactions (AR)	
					Treatment group = % AR	AR
8	Capobiango et al. (41)	Braz J Infect Dis, 2014	Brazil	Congenital toxoplasmosis in a reference center of Parana, Southern Brazil	PYR + SDZ = 16/29 (55.2%)	Neutropenia, n = 13 (44%) Thrombocytopenia, n = 2 (6.9%) Hepatities, n = 4 (13.8%)
9	Faucher et al. (42)	J Infect, 2012	Marseilles, France	Long-term ocular outcome in congenital toxoplasmosis: a prospective cohort of treated children	PYR + SDX = 10/121 (8.3%)	Neutropenia, n = 2 (1.7%) Anemia, n = 1 (0.8%) Nausea/vomiting, n = 1 (0.8%) Rash, n = 1 (0.8%) Discontinue treatment, n = 5 (4.1%)
10	Hotop et al. (43)	Clin Infect Dis, 2012	Germany	Efficacy of rapid treatment initiation following primary *Toxoplasma gondii* infection during pregnancy	PYR + SDZ = 25/119 (21%)	Nausea/vomiting, n = 24 (20%) Hypersensitivity, n = 1 (0.8%)
11	Lipka et al. (44)	Wiad Parazytol, 2011	Warsaw, Poland	Monitoring of plasma concentration of pyrimethamine (PYR) in infants with congenital *Toxoplasma gondii* infection - own observations.	PYR + SDZ/SDX = 11/24 (45.8%)	Neutropenia, n = 11 (45.8%)
12	Schmidt et al. (45)	Arch Dis Child, 2006	Denmark	The national neonatal screening programme for congenital toxoplasmosis in Denmark: results from the initial four years, 1999-2002	PYR + SDZ = 7/48 (14.6%)	Neutropenia, n = 6 (12.5%) Elevated bilirubin, n = 1 (2.0%)
13	McLeod et al. (46)	Clin Infect Dis, 2006	Chicago, USA	Outcome of treatment for congenital toxoplasmosis, 1981-2004: the National Collaborative Chicago-Based, congenital toxoplasmosis study	PYR + SDZ: a) Group 1: 2 months = 21/57 (37%) b) Group 2 6 months = 20/59 (34%)	a) Group 1: Neutropenia, n = 21 (37%) b) Group 2: Neutropenia, n = 20 (34%)
14	Villena et al. (47)	Scand J Infect Dis, 1998	Reims, France	Pyrimethamine-sulfadoxine treatment of congenital toxoplasmosis: follow-up of 78 cases between 1980 and 1997. Reims toxoplasmosis group.	PYR + SDX = 1/78 (1.3%)	Rash, n = 1 (1.3%)
15	Mombro et al. (48)	Eur J Pediatr, 1995	Torino, Italy	Congenital toxoplasmosis: 10-year follow up	PYR + SMP = 3/6 (50%)	Anemia, n = 3 (50%)
16	Guerina et al. (49)	N Engl J Med, 1994		Neonatal serologic screening and early treatment for congenital *Toxoplasma gondii* infection	PYR + SDZ = 15/47 (31.9%)	Neutropenia, n = 7 (14.9%) Anemia, n = 7 (14.9%) Rash, n = 1 (2.1%)

PYR = Pyrimethamine; SDX = Sulfadoxine; SDZ = Sulfadiazine; SMP = Sulfamide; SMX = Sulfamethaxazole; TMP = Trimetroprim

Recurrent or progressive disease affects 20-80% of patients and can occur because the encysted form of organism persists throughout life and remains in the neuroretina of the host (16-18). Soheilian et al. (25) showed that the rate of relapse in a period of 20 months, was significantly lower (6.6%), in a group of patients treated with oral TMP-SMX (160-800 mg) once every three days, as compared to 23.8% in a group without prophylaxis. Atovaquone is an alternative that can be considered as it is equally effective, with good patient compliance and has fewer side effects than TMP-SMX (29). Larger placebo-controlled trials are needed to validate the benefits of prophylaxis in ocular toxoplasmosis and the efficacy of atovaquone as an alternative to anti-folates. We, however, felt this patient may benefit from prophylactic treatment with atovaquone to preserve vision and reduce ocular morbidity after taking into consideration her allergic profile.

Conclusion

Individuals with ocular toxoplasmosis who cannot tolerate oral treatment might consider intravitreal injections of clindamycin and subconjunctival dexamethasone.

Competing interests

The authors declare that they have no competing interests.

Informed Consent

Written informed consent was obtained from the patient in this case report.

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