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NEURORETINITIS AS A MANIFESTATION OF OCULAR TOXOPLASMOSIS: A CASE REPORT

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ABSTRACT
Background:
Neuroretinitis is an inflammatory condition characterized by acute vision loss, optic nerve head (ONH) edema and macular star pattern exudate. It is commonly caused by *Bartonella* infection. This is a rare case of patient with neuroretinitis caused by *Toxoplasma* infection.
Case Presentation:
A 48-year-old female patient came with sudden blurred vision on right eye in the last one week, with a history of fever and stomach pain 2 weeks before. Right eye was unremarkable. Physical examination of left eye showed decreased visual acuity (5/20), decreased color vision, and relative afferent pupillary defect. Posterior segment of left eye showed edema of ONH and macular star. OCT of left eye revealed intraretinal fluid and increased RNFL and ILM-RPE thickness. Visual field examination of left eye showed central scotoma. Laboratory test result showed increased erythrocyte sedimentation rate (ESR) (66 mm/H) and procalcitonin level (0.242 ng/mL), and reactive IgM toxoplasma. Patient was treated with high dose methylprednisolone and oral antiparasitic drugs. After 2 weeks of treatment, there was significant improvement of patient's visual acuity, color vision and ONH
Conclusion:
Neuroretinitis is a less common manifestation of ocular toxoplasmosis. Awareness of the specific causes of neuroretinitis will lead to prompt clinical diagnosis and treatment, which will have a high chance of good outcome.
Keyword: *neuroretinitis, toxoplasma, ocular toxoplasmosis, macular star, infectious optic neuropathy*

BACKGROUND

Neuroretinitis is an inflammatory condition which is characterized by acute vision loss associated with optic nerve head (ONH) edema and exudates in the macula that forms a macular star pattern. Neuroretinitis is usually caused by infection or post viral autoimmune process. Neuroretinitis frequently associated with cat-scratch disease, which is caused by *Bartonella quintana* or *Bartonella henselae*. There are other infectious etiologies of neuroretinitis, including rubeola, toxoplasmosis, herpes simplex, varicella, tuberculosis, Lyme disease, leptospirosis, syphilis, various fungi, and multiple viral illnesses.[1]

In neuroretinitis, optic disc edema may be caused by the intraocular inflammation. The visual acuity in neuroretinitis is caused by vitreous inflammation and secondary changes in the macula. Swelling of the peripapillary retina may be observed in patients with anterior optic neuritis. Lipid exudates in a star configuration may also develop in the macula of the affected eye.[2]

Neuroretinitis has no gender predilections and can affect persons of all ages, although it occurs most often in the third and fourth decades of life. Neuroretinitis is usually a self-limited disorder with a good visual prognosis when treated promptly.[3] On the other

hand, Toxoplasmosis is an intracellular parasitic infection caused by Toxoplasma gondii with variable prevalence among geographical regions of the world. It is usually asymptomatic in immunocompetent patients. Toxoplasmosis can affect several organs, including the eye. In rare cases, toxoplasmosis can demonstrate an ocular manifestation such as focal necrotizing retinitis, vitritis, and anterior uveitis. Secondary complications of ocular toxoplasmosis include retinal perivasculitis.[4]

Ocular Toxoplasmosis can manifest in several forms. Ocular toxoplasmosis in the form of retinochoroiditis can account for up to 85% of all infectious causes of posterior uveitis. Its hallmark sign is a focal necrotizing retinitis associated or not with vitritis and anterior uveitis. Regardless of whether it is treated or not, retinal necrosis heals by leaving a pigmented retinochoroidal scar. Toxoplasma-induced retinal choroiditis can also manifest itself as multiple gray-white punctate lesions deep in the retina. Optic nerve toxoplasmosis is a less common presentation and is believed to occur in 5.3% to 16.5% of all ocular toxoplasmosis. Involvement of the optic nerve typically occurs next to or far from an active retinochoroiditis lesion. It can also present without an active or scarred lesion as papillitis or neuroretinitis.[5]

The diagnosis of ocular toxoplasmosis is most often based on the presence of characteristic clinical findings, which include focal retinochoroiditis, an adjacent or nearby retinochoroidal scar, and moderate to severe vitreous inflammation. However, a variety of less common “atypical” presentations may be unfamiliar to clinicians, which can both delay diagnosis and treatment. Patients who are immunocompromised or elderly may, for example, present with large, multiple and/or bilateral lesions. Other unusual manifestations include punctate outer retinal toxoplasmosis, retinal vasculitis, retinal vascular occlusions, rhegmatogenous and serous retinal detachments, a unilateral pigmentary retinopathy mimicking retinitis pigmentosa, neuroretinitis and other forms of optic neuropathy, and scleritis. Although in the past most cases of ocular toxoplasmosis were considered to result from reactivation of a congenital infection, it is now believed that postnatally acquired infection accounts for many cases of this disease. With appropriate use of antiparasitic therapy, the visual prognosis for patients with both typical and atypical forms of ocular toxoplasmosis may be good.[6] This case report describes a patient with neuroretinitis caused by toxoplasma infection to raise awareness among clinicians of neuroretinitis as a rare manifestation of ocular toxoplasmosis

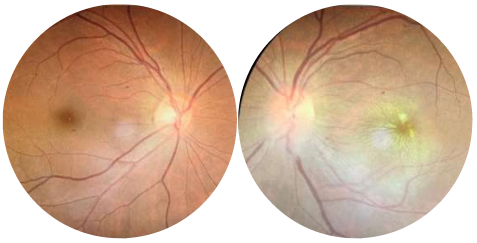
CASE PRESENTATION

A 48-year-old female patient came to outpatient clinic with sudden blurred vision on right eye since one week before. Blurred vision was described by the patient as looking through fogged windows. There is a history of 3-days fever 2 weeks before, with stomach discomfort but without vomiting or diarrhea. There was no complaint of red eye, double vision, ocular pain, or headache. The patient also said to have owned a cat at home, which was originally a stray cat that she took home and the cat was never vaccinated. There was no history of other illness, past medication, and previous surgery.

From general examination, the patient’s vital sign was within normal limit, with no enlarged lymph nodes, myalgia, stiff neck, painful swallowing or abdominal pain. The patient’s visual acuity at her first visit was 6/6 on right eye and 5/20 on left eye. Intraocular pressure was 18,5 mmHg

on both eyes. Color vision examination using Ishihara test was 14/14 plate on right eye, and 1/14 plate on left eye. Ocular motility on both eyes was normal with no pain within movement.

The patient's anterior segment of both eyes showed rounded pupils, isochoric 3 mm diameter, normal light reflex, and left eye relative afferent pupillary defect. Posterior segment of left eye showed hyperemic and blurred margin of ONH, with peri macular exudate forming a macular star pattern (Fig. 1). Posterior segment of right eye was within normal limit.



(A) (B)

Figure 1. Initial fundus examination showed normal right eye (A), left eye showed ONH edema and macular star (courtesy of RSUD Dr. Soetomo)

Optical coherence tomography (OCT) of ONH showed an increase of retinal nerve fiber layer (RNFL) thickness in left eye and within normal limit in right eye (Fig. 2). Macula OCT showed increased inner limiting membrane-retinal pigment epithelium (ILM-RPE) thickness in left eye and normal thickness in right eye (Fig. 3). Left eye macular OCT also showed subretinal fluid below RPE and decreased average ganglion cell layer (GCL) and inner plexiform layer (IPL) thickness.

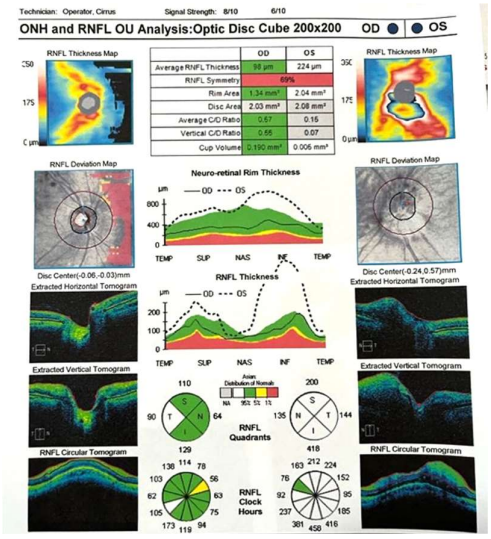


Figure 2. Initial OCT of ONH showed increased RNFL thickness in all quadrants of left eye and normal right eye (courtesy of RSUD Dr. Soetomo)

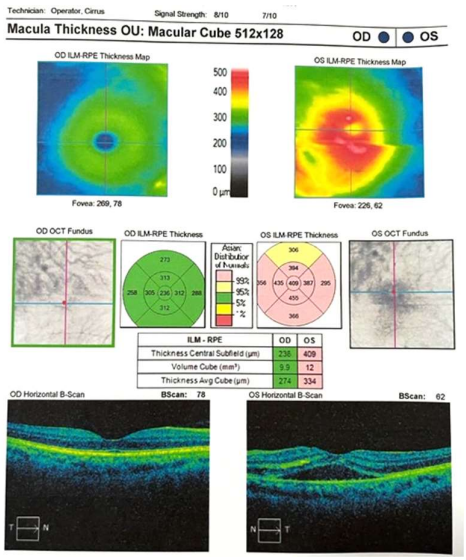


Figure 3. Initial macular OCT showed intraretinal fluid and increased thickness of left eye's ILM-RPE, with normal right eye (courtesy of RSUD Dr. Soetomo)

Visual field examination was done using Humphrey Field Analyzer (HFA) and the result showed central scotoma on left eye and normal right eye (Fig. 4). Although during HFA examination of left eye, the patient had a difficulty of focusing straight to the target, because she cannot see the central target due to her left central scotoma, therefore the fixation

loss of left eye HFA examination was high.

The patient's blood laboratory tests were done to rule out infective and autoimmune causes. Her blood laboratory examination showed normal full blood count, normal liver and renal function test, with increased cholesterol (256 mg/dL) and LDL cholesterol (185 mg/dL). The patient's blood glucose status was also slightly abnormal, with fasting glucose level 165 mg/dL, post prandial blood glucose 161 mg/dL, and HbA1C 6,7%. Autoimmune marker (C3, C4) was within normal limit. However, the patient's TORCH test showed Immunoglobulin (Ig) M serology for Toxoplasma was reactive (4.039 AU/mL), with IgG Toxoplasma non-reactive (1,821 AU/mL). This infection status was also showed on the patient's increased erythrocyte sedimentation rate (ESR) (66 mm/H) and procalcitonin level (0.242 ng/dL), which indicated local infection. The laboratory test result for HIV infection in this patient showed non-reactive.

Based on clinical and ancillary tests result, the patient was diagnosed with Left Eye Neuroretinitis due to Toxoplasma Infection. Patient was admitted to hospital to be given Methylprednisolone 250 mg intravenously every 6 hours, as well as oral neuroprotector (Vitamin B complex 2x1). A consultation with Internal Medicine Department was done regarding the patient's toxoplasma infection, and the patient was given oral anti Toxoplasmosis drug for 2 weeks, which was Clindamycin 3x300mg and Pyrimethamine 3x25mg. The patient was also given Folic Acid 3 times daily by internal medicine department to prevent bone marrow prevent bone marrow suppression, which may result from pyrimethamine therapy.

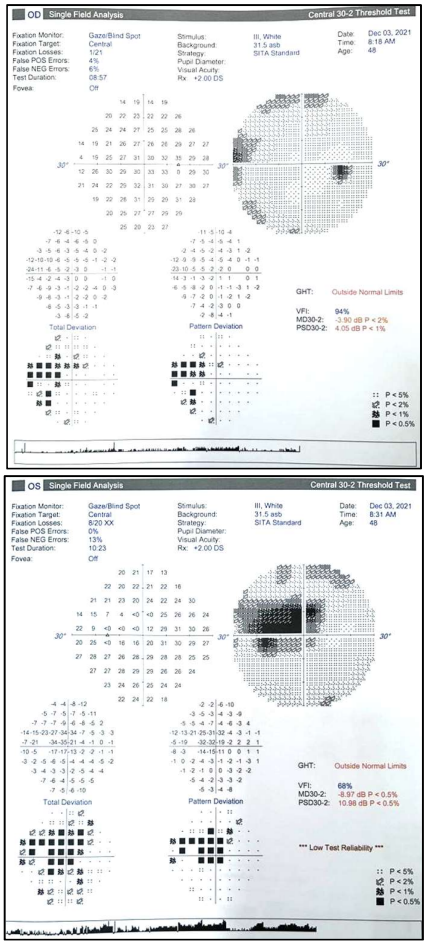
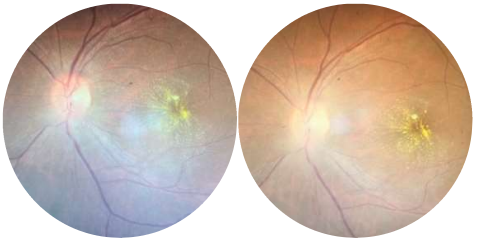


Figure 4. Visual field examination showed normal on right eye (top) and central scotoma on left eye (bottom) (courtesy of RSUD Dr. Soetomo)

After five days of treatment, the patient showed clinical improvement. The visual acuity of left eye was improved to 5/10. The patient's weight was 64kg. Methylprednisolone treatment was then continued orally 32mg twice daily every 12 hours (1mg/kg body weight/day) and the patient was discharged from hospital ward.

After one week of treatment, the visual acuity of the patient's left eye remained the same (5/10). The posterior segment of left eye showed blurred margin of ONH but the color was slight hyperemic, and a macular star pattern was still showed (Fig. 5). The Ishihara test of left eye after one week of treatment

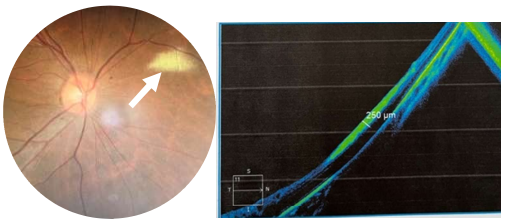


(A) (B)

Figure 5. Posterior segment of left eye after one week (A) and two weeks (B) of treatment showed slight improvement of ONH hyperemia with macular star still visible (courtesy of RSUD Dr. Soetomo)

The head and orbital focused MRI with and without contrast of the patient showed no abnormalities on right of left retroorbital area. The MRI also showed no infarct, mass or infection in the brain parenchymal area

Clinical findings after two weeks of treatment, showed further improvements. The patient claimed to see more clearly form her left eye, and the left visual acuity was 5/8 cc S-+0.25 C-1.00 X90 → 5/6. The Ishihara test of left eye showed 3/14 plate. The posterior segment of left eye still showed macular star, but the ONH was not hyperemic and the blurry margin of ONH was decreased (Fig. 5).



(A) (B)

Figure 6. A) Posterior segment of right eye two weeks after treatment showed retinal scar (arrow) on superomedial quadrant. B) HD- 12 Line OCT of the retinal scar area showed increased thickness of nerve fiber layer. (Courtesy of RSUD Dr. Soetomo)

However, during the follow-up fundus examination on two weeks after treatment, a retinal scar was found on right eye, on the superomedial quadrant of the retina (Fig. 6). The right eye retinal scar was confirmed through OCT where it showed increased thickness of the nerve fiber layer on the area of retinal scar (Fig. 6).

The OCT of the patient, 2 weeks after treatment showed an increase of RNFL thickness in left eye and within normal limit in right eye (Fig. 7), however, the thickened ONH was limited to only on superior, inferior and lateral quadrant. Macula OCT of left eye showed no more intraretinal fluid, with slight decreased of ILM-RPE thickness (Fig. 8) and also slight decreased of average GCL and IPL thickness. The patient's OCT result 2 weeks after treatment showed improvements compared to the patient's initial OCT.

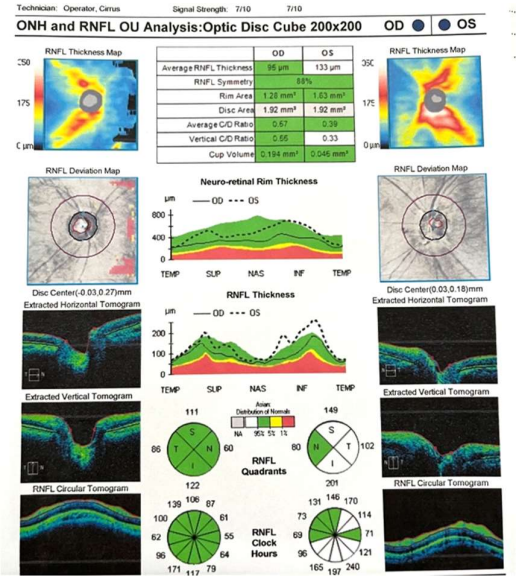


Figure 7. OCT 2 weeks after treatment showed increased RNFL thickness of left ONH, but only on superior, inferior and temporal quadrants. Right eye remained normal (Courtesy of RSUD Dr. Soetomo)

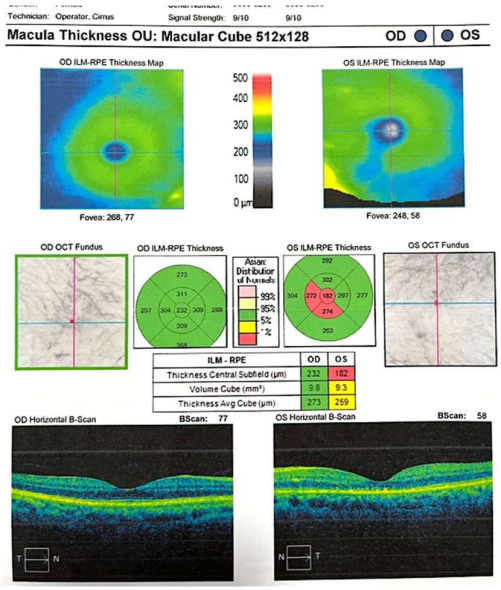


Figure 8. Macular OCT two weeks after treatment showed no intraretinal fluid and slight decreased of left eye ILM-RPE layer, with normal right eye (Courtesy of RSUD Dr. Soetomo)

Because of the improvements of the patient's clinical condition, after 2 weeks of treatment, the methylprednisolone dose given to the patient was tapered off to 32mg and 16mg respectively every 12 hours. The patient was advised to come for routine follow up every 1 week while she was still given oral steroid. The HFA examination is planned to be repeated after 1 month of treatment.

DISCUSSION

The clinical findings of the patient in this case were consistent with the diagnosis of neuroretinitis, which is an inflammatory condition characterized by acute vision loss associated with optic nerve head (ONH) edema and exudates in the macula that forms a macular star pattern.[1] The main mechanism of neuroretinitis is inflammation of the optic disc vasculature, which results in fluid exudation into the retina's periphery.[7]

However, in addition to neuroretinitis, other conditions such as hypertensive retinopathy, papilledema, anterior ischemic optic neuropathy, diabetic papillopathy, posterior vitreous traction, disc juxtapapillary tumors (angioma, melanoma), and toxic condition can also result in optic disc edema with a macular star.[7] A lumbar puncture and imaging along the optic nerve's path (brain MRI, CT scan) should be part of the workup for acuity, visual field loss, and genuine optic disc edema.[8]

Clinical state is the basis for diagnosing neuroretinitis. Some patients report having an eye soreness that worsen with eye movements. When first examined, a patient's visual acuity may range from 20/20 to light perception. Patients with neuroretinitis may experience color vision loss and visual field defect, typically cecocentral scotomas.[3]

The funduscopic appearance in neuroretinitis largely depends on when the examination is performed, ranging from solitary optic disc edema, hemorrhages in the peripapillary nerve fiber layer, and peripapillary exudative retinal detachment. The characteristic macular exudates normally occur after 9 to 12 days, and disc edema is usually starting to lessen by then. After a few months, the exudates become less pronounced and finally dissolve entirely, leaving behind residual sub-foveal retinal pigment epithelium deficiencies. At first, the star figure is highly defined and spike-like. Optic disc edema usually goes away in 8 to 12 weeks. Eventually, the disc might revert to its original state or show signs of gliotic alterations and/or pallor.[7]

Numerous agents, including Bartonella henselae, TB, salmonella, toxoplasmosis, syphilis, measles, rubella, varicella, and many more, can be linked to neuroretinitis. Cat scratch disease (CSD) is the most common cause of neuroretinitis, accounting for two thirds of cases.[7]

The clinical or pathological condition caused by Toxoplasma gondii is referred

to as toxoplasmosis. For clinical purposes, toxoplasmosis can be conveniently divided into five infection categories: (1) acquired by immunocompetent patients, (2) acquired during pregnancy, (3) acquired congenitally; and (4) acquired by or reactivated in immunodeficient patients, and (5) including ocular infections.[9]

Toxoplasma gondii is an obligate intracellular parasite, which comes in three different forms: tachyzoite (a proliferative form), cyst (which contains bradyzoite), and oocyst (which contains spozoite).The domestic cat serves as the ultimate host, excreting millions of oocysts in their faeces that can live in soil for extended periods of time. Humans and other warm-blooded mammals serve as intermediate hosts, contracting the infection through handling or consuming tainted food or water, and consuming undercooked meat from animal intermediate hosts, such as sheep and pigs.[10] The parasites create tissue cysts in the human host, usually in the brain, eyes, heart, and skeletal muscle. These cysts may last the host's entire life. Serology is typically used to make the diagnosis, albeit stained biopsy specimens may show tissue cysts.[11]

One of the organs that toxoplasmosis might damage is the eye. *Toxoplasma gondii* infections can manifest as acute systemic infections in approximately 10–20% of immunocompetent persons. These infections usually appear 5–23 days following introduction to the organism. These patients usually exhibit bilateral, symmetrical, nontender cervical adenopathy, flu-like symptoms, and potentially vision impairment.[10]

In most cases, ocular toxoplasmosis appears in the second or fourth decade of life.[12] The uncommon disorder known as toxoplasmic optic neuropathy is frequently accompanied by subacute vision loss, optic nerve enlargement, and occasionally a macular star (neuroretinitis).[13] Macular lesions are typically the cause of visual impairment. Although it is less common, involvement of the optic nerve can result in significant visual field abnormalities and loss of color vision. Blurred vision is the primary sign of ocular toxoplasmosis and is linked to symptomatic vitreous inflammation in active lesions.[14]

Scars are indicative of dormant lesions of ocular toxoplasmosis, which usually affect the posterior pole of a single eye. They are frequently found on routine examinations without any history or indications of active retinochoroiditis. They can be single, numerous, or satellite to another pigmented retinal scar. [14]

The following are examples of atypical presentations of ocular toxoplasmosis: rhegmatogenous and serous retinal detachments; neuroretinitis and other forms of optic neuropathy; peripheral retinal necrosis; scleritis; massive granuloma; multifocal punctate lesions; retinal vasculitis; unilateral pigmentary retinopathy mimicking retinitis pigmentosa; and so on.[15]

Toxoplasmosis-related optic nerve involvement was divided into five categories: (1) Juxtapapillary retinochoroiditis, which is a retinochoroidal lesion adjacent to the swollen optic disc; (2) Pure Papillitis, which is a swollen optic disc and sheathing of the peripapillary veins in the presence of a healed toxoplasmic retinochoroiditis lesion, (3) Neuroretinitis, which is characterized by a swollen optic disc, papillo-macular or serous macular detachment of the retina with hard exudates at the macula, (4) Distant lesion: enlarged optic disc with a distant active lesion; and (5) Mixed lesion: multiple types of involvement that were previously documented coexisting.[16] The most common type of optic nerve involvement in cases of ocular toxoplasmosis was

optic nerve edema combined with a distant active lesion. The second most often observed lesion type was juxtapapillary retinochoroiditis. The majority of cases involved monocular involvement, with a favorable visual prognosis.[17]

Multimodal imaging techniques include fundus fluorescence angiography (FFA), optical coherence tomography (OCT), and B-scan ultrasonic imaging can validate clinical findings. FFA can be used to track the presence of inflammation (e.g., vasculitis or active retinitis). Serological testing, such as serum anti-Toxoplasma titers of IgM and IgG, may be required to support the diagnosis in cases where clinical symptoms and any imaging support are insufficient to reach a firm diagnosis. PCR of aqueous and vitreous samples or toxoplasma gondii antibody titers in ocular fluids are two additional recently developed methods with excellent sensitivity and specificity to confirm the diagnosis.[14]

IgM levels in acute systemic toxoplasma infections often peak within a month and drop before six to nine months. IgG has a low positive predictive value and should not be interpreted as an active toxoplasmic infection because it can be detected up to 6-7 weeks after IgM and is detectable for the duration of the patient's life. Two serological patterns can be indicative of patients presenting with ocular disease in the context of acute infection: (1) elevated titer of T. gondii-specific serum IgM antibody and negative IgG (repeat of both anti-Toxoplasma IgM and IgG is required to rule out a possible cross-reactivity); (2) positive serum specific IgG and IgM antibodies, though IgM negativity does not rule out the diagnosis of ocular toxoplasmosis (ocular manifestations typically appear months after the initial infection, at which point IgM may no longer be present).[14]

In this patient, the clinical and laboratory findings support the diagnosis of neuroretinitis and can be classified as an active ocular toxoplasmosis. However, further diagnostic examination of Toxo-IgG avidity, Toxo-IgG aquous humor and Toxo-PCR aquous humor was not done in this patient due to the lack of test availability in this hospital. Therefore, the confirmed diagnosis of acute ocular toxoplasmosis disease cannot be known.

The choice of treatment for neuroretinitis depends on the underlying inflammatory or infectious diseases.[3] Corticosteroids and antiparasitic medication are used in conjunction to treat toxoplasmosis-associated optic neuropathy. Pyrimethamine is administered as part of the conventional treatment at loading doses of 100 mg on day 1 and 50 mg/day (25 mg in children), along with 4 g/day of sulfadiazine. A supplement of folinic acid (25 mg twice or three times a week) is given to avoid bone marrow suppression that could arise from pyrimethamine treatment.[18] Antibiotics and corticosteroids should be given right away in cases of toxoplasma-induced neuroretinitis in order to limit inflammation and potential optic nerve injury.[19]

CONCLUSION

Neuroretinitis is a less common manifestation of ocular toxoplasmosis. When treated and managed promptly through systemic steroid and antiparasitic drug, neuroretinitis caused by toxoplasmosis can have good outcome, as displayed in this case report. Awareness of the specific causes of neuroretinitis will lead to prompt clinical diagnosis and treatment, which will have a high chance of good outcome.

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