CASE REPORT

CHALLENGE IN TREATING OPTIC NEURITIS IN PATIENT WITH CEREBRAL TOXOPLASMOSIS RELATED TO IMMUNOCOMPROMISED CONDITION

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ABSTRACT

Introduction: *This study aimed to discuss challenge in treating optic neuritis in a patient with cerebral toxoplasmosis related to an immunocompromised condition.*

Case Report: *A 28-year-old female complained of blurred vision and double vision 2 weeks before admission, accompanied by headache, low extremities weakness, dysphonia, and dysphagia. The visual acuity of both eyes was 6/30 and worsened to 6/60 in a couple of days. Anterior segment examination revealed anisocoria pupil, and RAPD was positive in the left eye. Funduscopic examination showed a blurry margin and hyperemia of the optic nerve head. There was impaired eye movement, indicating oculomotor and abducens nerve palsies. High titer of IgG Antibody Toxoplasma (264) and very low titer of CD4 (<50) with non-reactive HIV rapid test were found in laboratory findings. Multiple ring enhancement was shown in MRI finding. Unfortunately, the patient passed away during hospitalization due to respiratory failure.*

Discussion: *Toxoplasmosis-associated optic neuritis is rare and usually becomes potentially serious. Although parasite detection by microscopy and bioassay is considered the gold standard for the diagnosis of toxoplasmosis, clinical diagnosis relies more on serological examination methods. The high proportion of deaths from this disease is mostly caused by late diagnosis of the infection.*

Conclusion: *Optic neuritis that is accompanied by systemic disorders needs special attention and comprehensive treatment among multidisciplinary divisions, especially in the immunocompromised condition. Early detection and primary prevention are important to improve prognosis and survival rate.*

Keywords: *optic neuritis, cerebral toxoplasmosis, immunocompromised state*

INTRODUCTION

Optic neuritis is an important cause of potentially irreversible visual impairment.[1] Optic neuritis refers to inflammation of the optic nerve, which is a frequent cause of acute optic nerve injury in children and adults. Optic neuritis can affect any part of the nerve. When affecting the posterior portion of the optic nerve, the optic nerve papillae appear normal when the patient experiences vision loss (retrobulbar optic neuritis); when inflammation involves the anterior portion, the optic nerve papillae appear edematous (papillitis).[2,3]

The exact mechanism of acute optic neuritis has yet to be clearly identified. Optic nerve infiltration usually occurs along with neurological or systemic signs and symptoms.[4,5] Infections from bacteria, spirochetes, viruses, fungi, and protozoa (Bartonella, Rickettsia, Coxsackievirus

B, human immunodeficiency virus (HIV), histoplasmosis, and toxoplasmosis) in the optic nerve can cause optic neuritis.[2]

Toxoplasmosis is a central nervous system (CNS) infection caused by *Toxoplasma gondii* (*T. gondii*), and it can spread throughout the body.[6] Toxoplasmosis is a common infection whose prevalence is estimated at 30% worldwide.[7] Clinical manifestations that can arise in cerebral toxoplasmosis are headache, fever, hemiparesis, ataxia, cranial nerve disorders involving impaired ocular movement, seizures, as well as involuntary and rigidity movements. Clinical features of ocular toxoplasmosis are retinal scars, vitritis, optic neuritis, and retinal detachment. Toxoplasmosis is generally benign but has the potential to be severe in immunocompromised patients.[8]

The purpose of this case report is to discuss the diagnosis and prognosis of patients with bilateral optic neuritis with partial ophthalmoplegia caused by paresis of N.III and paresis of N.VI (multiple cranial nerve palsy) due to suspected cerebral toxoplasmosis with immunocompromised condition.

CASE ILLUSTRATION

A 28-year-old female patient from the Neurology Department with diagnosis Multiple cranial nerve palsy due to suspected neuromyelitis optica spectrum disorder (NMOSD) with differential diagnosed infratentorial Cerebral space occupying process (SOP) due to Primary cerebral tumor and metastatic process was consulted to Ophthalmology department because the patient complained of double and blurred vision 2 weeks before hospital admission.

The patient complained there was double and blurred vision, which was only felt when looking far away and waking up for 2 weeks before admission followed by glare and pain when looking. One week later patient complained of difficulty swallowing, shortness of breath, and cough. There were no complaints of red eyes, tearing, or muttering. Initially, the patient complained of hoarse voice and sore face followed by headaches and weakness in both legs 1 month. In the last 1 month, the patient also experienced weight loss. The patient's weight decreased by 10 kg within 1 month. There was no history of ocular trauma, eye surgery and spectacle use. There was no history of systemic disease and family history with same complained was denied. The patient had a history of keeping cats and dogs since childhood.

From general condition, the patient was completely conscious with normal vital signs. Vesicular breath sounds throughout the lung fields. Glove and stocking-type hypesthesia were found.

An examination of the cranial nerve at N. V showed corneal sensibility and sensory examination within normal limits. An examination of N. VII demonstrated UMN-type paresis on the right side of the face. An examination of N. IX and X in the patient yielded positive dysphonia results. On examination of N. XII, UMN-type parese dextra (tongue atrophy) was found.

From ophthalmological examination, visual acuity in both eyes was 6/30, using the Snellen chart. It was found that the pupil size of the right eye was 3mm and the left eye was 5mm, the light reflexes of both pupils were positive but slower in the left eye, and there was a relative afferent pupillary defect (RAPD) in the left eye.

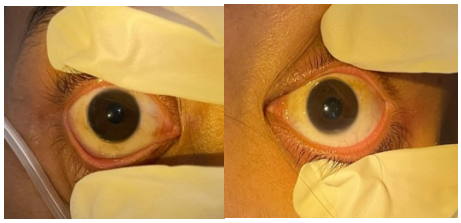

Figure 1. Anisocoria was noted. Dilated pupil in the left eye. No dyschromatopsia was noted.

Visual field using confrontation test revealed superotemporal defect on the left eye and superonasal in the right eye. The limitations of the eye movement of both eyes were seen on superotemporal, temporal, and inferotemporal directions.

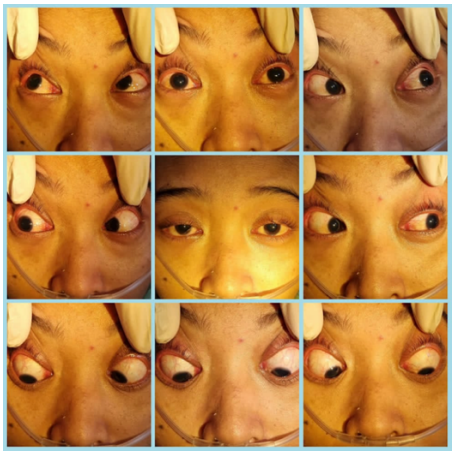

Figure 2. Eye movement examination: limitation of both eye movements seen on superotemporal, temporal, and inferotemporal directions

On funduscopic examination, fundus reflexes were positive in both eyes. The optic nerve got swelling and hyperemic in all quadrants, so the CD ratio was difficult to evaluate. There were no focal exudates, scar tissue, retinal hemorrhages, or vitritis in the vitreous.

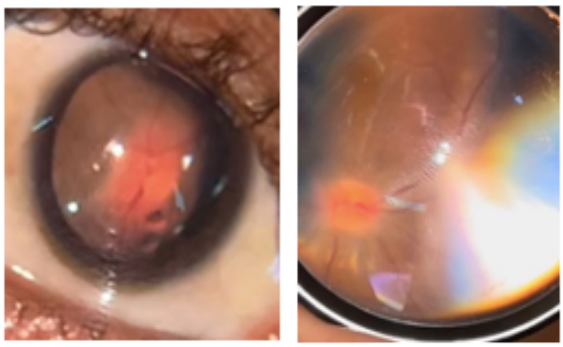

Figure 3. Fundus photos of both eyes. The margin of the N. II ODS optic nerve head appeared blurry.

Laboratory examination showed that Anti-CMV IgG was positive (95.7), Anti-HSV-1 IgM and IgG were positive (67/>200); Anti HSV-2 IgM was positive (110.5), Anti Rubella IgG was positive 32.55; VDRL was non-reactive, TPHA was non-reactive; Anti-Toxoplasma IgM was negative, Anti-Toxoplasma IgG was positive (0.488/264), and CD4 <50 but for HIV examination was non-reactive. This examination was carried out because there was a suspicion of an immunocompromised condition due to various infections found in the patient. The patient also underwent a chest X-ray examination, and an image of pneumonia was obtained.

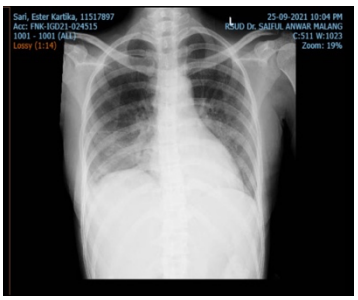

Figure 4. Chest X-ray image. Infiltrates were found in both lung fields.

A Head MRI with contrast on the 7th day of treatment showed the following results:

- Multiple intraaxial rim-enhanced lesions in bilateral fronto-temporoparietooccipital lobes, bilateral centrum semiovale, right corona radiata, bilateral external capsule, bilateral thalamus, mesencephalon, pons, cerebellum suspect et causa toxoplasmosis; and
- Looping of right AICA grade III with CHAVDA classification.

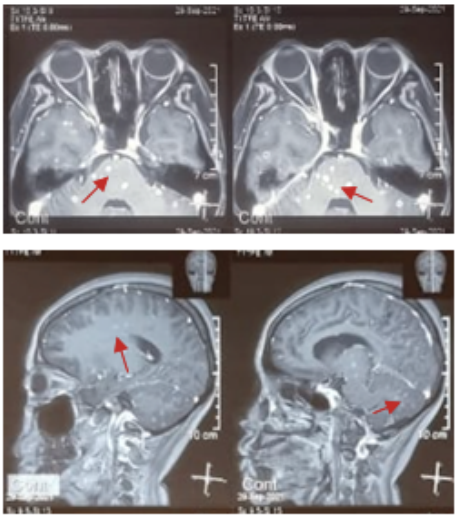

Figure 5. Head MRI examination result. Multiple ring enhancement was found in bilateral fronto-temporoparietooccipital lobes, bilateral centrum semiovale, right corona radiata, bilateral external capsule, bilateral thalamus, mesencephalon, pons, and cerebellum.

The patient's examination on the 10th day showed a decrease in visual acuity to 6/60 in both eyes. However, the other ophthalmologic status still showed the same results as the previous examination.

The patient was treated together with the neurology department and diagnosed with Multiple Cranial Nerve Palsy due to suspected Toxoplasmosis Cerebri dd Tuberculoma, Inferior paraplegia UMN Type due to suspected NMOSD dd Leptomeningeal Metastases, Hypokalemia, Leukocytosis and Immunocompromised state. The patient was given WidaKN2 infusion therapy for 2 cycles, followed by maintenance of Normal Saline 0.9 20 drops per minute, Paracetamol 3x500 mg orally, loading Pyrimethamine 200mg, and Clindamycin 4x600mg.

The patient was also consulted to Pulmonology and Respiratory Department and was diagnosed with Pneumonia (HAP) due to Acinetobacter baumannii and impending respiratory failure type 2. The patient was given oxygen via NRBM 8 lpm, Combivent nebulization 3x1, 2x80mg Gentamicin injection, methylprednisolone injection 1x31.25mg, Cefixime 2x200mg per oral for 7 days, Theophylline 2x1 per oral, and Codeine 3x10mg per oral.

Based on the history taking and examinations, the patient was diagnosed with ODS optic neuritis and optic neuropathy with partial ophthalmoplegia caused by paresis of N.III and paresis of N.VI (multiple cranial nerve palsy) with suspected toxoplasmosis and immunocompromised state with the differential diagnosis papiloedema due to increased intracranial pressure.

The patient received treatment of neuroprotectant from the neuro-ophthalmology division along with other therapies from the neurology and pulmonary disease department. The patient passed away on the 11th day of treatment, allegedly due to respiratory failure.

DISCUSSION

Optic neuritis a rare and uncommon manifestation of toxoplasmosis, which is characterized by a gradual loss of vision and enlargement of the optic nerve. In certain cases, it may also be accompanied by a macular star, known as neuroretinitis. Treatment typically leads to a favorable prognosis for optic neuritis. However, the presence of systemic abnormalities in the patient, such as cerebral abnormalities, toxoplasmosis cerebri, or immunocompromised conditions, can exacerbate the condition. The degree of visual impairment in patients with optic neuritis can range from near-normal acuity to no light perception.

This study demonstrates anisocoric pupil size in the right eye and relative afferent pupillary defect (RAPD) in the left eye. RAPD is a clinical indicator utilized to identify abnormalities in the pupillary pathway on the afferent side. Optic neuritis is one of the possible causes of this condition.[15]

Cranial nerve dysfunction can occur due to lesions in its course from the intrinsic brainstem to its peripheral pathways. Multiple cranial nerve dysfunction is defined as the condition where two or more cranial nerves are affected. Mehta et al. discovered that the abducens cranial nerve (VI) had the highest occurrence of involvement among cranial nerve, followed by the oculomotor (III) and trigeminal (V) cranial nerves. The most common cause of involvement was found to be infection.[16]

Optic disc swelling may be seen on funduscopic examination in some patients during the active phase.[3] If a clinician observes substantial inflammation of the optic disc, hemorrhage in the optic disc, or ocular inflammation, they should examine the possibility of infection. [1]

Toxoplasmosis-associated optic neuritis is uncommon and typically has the potential to be severe. A retrospective study conducted by Eckert et al. explained that of 928 patients only 51 eyes (5.03%) had optic nerve involvement. Out of the 51 eyes, 22 eyes (43.1%) exhibited optic neuritis accompanied by active lesions located distant from the papillae, whereas 18 eyes (35.3%) with optic neuritis with lesions close to the papillae, 8 eyes (15.7%) showed more than one type of lesion simultaneously. Of these 8 eyes, 6 eyes (75%) demonstrated distant active lesions associated with neuroretinitis, while the remaining two (25%) displayed active lesions near the papillae associated with neuroretinitis. Pure papillitis without retinal lesions only occurred in 3 (5.9%) out of 51 eyes.[17]

A reduction in CD4 count (<50) in this patient signifies an immunocompromised condition and increases the risk factor for reactivation of latent tissue cysts containing toxoplasma parasites due to immune system deficiencies. This reactivation contributes to the emergence of *T. gondii* infection which manifests as neurological symptoms, including headache, disorientation, drowsiness, reflex changes, seizures, and hemiparesis.[18] Examination of the cranial nerves in this patient showed a lesion in N. VII due to paresis on the right side of the face. In HIV, clinical manifestations occur when the CD4 lymphocyte count is <100 cells/ml. The most common manifestation of HIV is encephalitis. Encephalitis occurs in approximately 80% of cases. The initial symptoms that appear are a headache and a focal neurological deficit.[19]

The patient's physical examination revealed the presence of hypesthesia with the glove and stocking type. Martinot et al. and Matsuura et al. have also reported cases of toxoplasma with patient symptoms in the form of hypesthesia.[12,13] Toxoplasmosis cerebri typically results in unifocal lesions, with diffuse lesions being a rare incidence. Clinical symptoms depend on the location and number of lesions. The most frequently complained of symptoms include headache (49-63%), fever (41-68%), focal deficit (22-80%), seizures (19-29%), confusion (15-52%), ataxia (15-25%), lethargy (12- 44%), cranial nerve weakening (12-19%), and visual disturbances (8-15%). Other manifestations may include dysarthria, cognitive impairment, increased intracranial pressure, and involuntary movements.[14]

Serological tests to determine the cause of infection must be carried out according to the suspected etiology.[20] The patient's serological examination yielded positive results for toxoplasmosis infection. Toxoplasmosis is a life-threatening opportunistic infection in immunocompromised patients. Diagnosing *T. gondii* infection in immunocompromised patients can be challenging. Although parasite detection by microscopy and bioassay is considered the gold standard for the diagnosis of toxoplasmosis, clinical diagnosis relies more on serological examination methods.[21]

Acute viral infection is a rare cause of isolated optic neuritis. Herpes simplex virus (HSV) may be involved in cases of acute optic neuritis, many of which coincide with inflammation of the retina, brain, or eye. HSV optic neuritis can occur concurrently with or following HSV encephalitis or retinal necrosis.[1]

Primary infection with *T. gondii* might lead to clinical manifestations in the eyes.[8] Toxoplasmosis usually manifests in the second to fourth decades of life.[9] Patients with optic neuritis usually range in age from 20 years to 50 years, with a higher prevalence in women. Common symptoms include acute loss of vision, scotoma, impaired color vision, and pain felt

when moving the eyeball.[4]

The patient has a long-standing history of pet ownership, specifically cats and dogs, dating back to their childhood. Toxoplasmosis has a complex epidemiology. This parasite is capable of infecting almost all warm-blooded animals and has a two-host life cycle. Domestic cats and other members of the *Felidae* family are the definitive hosts. Non-*Felidae* species, including dogs and humans, are intermediate hosts for *T. gondii*. However, *T. gondii* can also undergo asexual reproduction in *Felidae* animals that operate as intermediate hosts.[10]

Hosts can contract infections by ingesting tissue that contains cysts or by consuming water or food contaminated with oocysts.[10] Humans can also become infected through consuming raw or improperly cooked meat containing infectious tissue cysts or through the consumption of sporulated oocysts in fruits and vegetables or water contaminated with cat feces.[8]

Groups of severely immunocompromised patients are susceptible to developing cerebral toxoplasmosis.[22] Toxoplasma gondii infection induces strong innate and adaptive immune responses. While the innate immune response is important for controlling the early stages of infection, the adaptive immune response is critical for limiting parasite replication during later stages. Although CD8 T cells play an important effector role in controlling chronic infections, their maintenance depends on the essential help provided by CD4 T cells. [23,24]

Radiological imaging of the brain frequently shows multiple (67%) or single (33%) brain lesions often associated with edema. There is a tendency for involvement of the basal ganglia, corticomedullary junction or cerebral white matter.[25] CT scans usually demonstrate bilateral, multiple, hypodense ring enhancing lesions with surrounding edema in 60% to 70% of patients. The lesion may be solitary in 27% of patients. If the CT scan is normal during initial screening, MRI is recommended because it is more sensitive and can detect additional lesions in some cases.[21] On MRI examination, toxoplasmic encephalitis is often characterized by multiple ring-enhancing lesions in the cortex and/or basal ganglia. Although these are the two most common sites for *T. gondii* lesions, they can also be found both supra- and infra-tentorially.[25]

The patient was previously diagnosed with multiple cranial nerve palsy and suspected NMOSD. The cause of optic neuritis can be from demyelinating optic neuritis, which eventually progresses to clinically definitive Multiple Sclerosis (MS), or from an immune-mediated demyelinating disease affecting the optic nerve as part of Neuromyelitis Optica Spectrum Disease (NMOSD). [26] However, in this patient, the diagnosis was more likely to be Toxoplasma because the clinical condition was more suggestive of toxoplasmosis.

The results of trials by Petzold et al. recommend intravenous steroids, not to improve clinical outcomes, but to accelerate functional recovery of vision.[28] Methylprednisolone IV (1,000 mg daily for 3 days) followed by oral prednisone (1 mg/kg/day for 11 days) has been reported to improve vision and better short-term functional recovery.[29]

The combination therapy of pyrimethamine, clindamycin and steroids to this patient is expected to improve the clinical condition. Pyrimethamine is a drug that is specific for the tachyzoite stage of toxoplasma and can penetrate brain parenchyma. Pyrimethamine has a synergistic effect when combined with clindamycin and sulfadiazine. This combination is recommended as first-line therapy for toxoplasmosis cerebri in HIV patients. This patient received a loading dose of Pyrimethamine 200mg and Clindamicyn 4x600mg orally.[30]

Thus, a wide spectrum of clinical manifestations is possible with this disease, and radiological imaging of the brain is indicated to evaluate empiric therapy, including assessing for deterioration on neuroimaging, in addition to the clinical deterioration that occurs.[31]

Since the patient's CD4 counts were low and the disease progression was very rapid, especially for ocular disorders, special and comprehensive monitoring and evaluation is required across all patient-care departments. Quick coordination throughout divisions is also needed in treating toxoplasmosis cerebri patients who are immunocompromised.

Although respiratory failure was eventually identified as the cause of the patient's death, other theories contend that primary *Toxoplasma gondii* infection in immunocompromised patients can cause fatal clinical outcomes.[8] The high proportion of deaths in this disease is mostly caused by late diagnosis of the infection. Mortality related to Toxoplasmosis Encephalitis in HIV patients is almost 100% if there is a delay in therapy.[32]

CONCLUSION

Optic neuritis accompanied by systemic abnormalities requires special attention and comprehensive multidisciplinary treatment. Toxoplasmosis infection in immunocompromised states is a life-threatening opportunistic infection. Toxoplasmosis papillitis is a rare and potentially serious condition, so early detection and primary prevention in immunocompromised patients is important to improve prognosis and survival rates.

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