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CASE REPORT

REMARKABLE OUTCOME AFTER MANAGEMENT OF LINEZOLID INDUCED OPTIC NEUROPATHY ON MULTI DRUG RESISTANT TUBERCULOSIS PATIENT:A CASE REPORT

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ABSTRACT

Background: Toxic optic neuropathy (TON) is a group of medical disorders which can be defined by visual impairment due to optic nerve damage by a toxin. Long term of linezolid treatment as one of antituberculosis therapy (ATT) can trigger Linezolid induced toxic optic neuropathy (LION). It is characterized by papillomacular bundle damage, cecocentral scotoma, and reduced of color vision.

Case Illustration: A 48 years old woman reffered from Pulmonology department complained blurred vison of both eyes since 7 days before. The patient has been diagnosed with MDR-TB since May 2022 and has been consuming ATT for 8 months. One of the ATT regimen were Linezolid 450mg once a day. BCVA of both eyes were 3/60 and 2/60 . Ishihara in right eye were 4/38, and 2/38. Funduscopy examination revealed bilateral optic disc edema with increasing of RNFL thickness in both eyes in OCT and bilateral central scotoma in HFA. The patient was diagnosed with linezolid induced optic neuropathy and replaced linezolid with another ATT. After 6 months of follow-up, BCVA in the both eyes became 5/5 with improving of color vision became 35/38 in both eyes. OCT and HFA examination revealed no thickening of RNFL thickness and no visual field defect.

LION is a complication associated with prolonged use of linezolid, regardless of the dose received, and reversible in most cases but the exact duration of symptom resolution following drug discontinuation remain unknow. However, the presence of other illnesses can impede the recovery.

Conclusion: Monitoring of visual function is important in patients on long-term linezolid therapy for early recognition of toxicity and discontinuation of the drug resulting in complete visual recovery.

***Keywords**: tuberculosis, multidrug resistant tuberculosis, linezolid, toxic optic neuropathy*

INTRODUCTION

Toxic optic neuropathy (TON) is a group of medical disorders which can be defined by visual impairment due to optic nerve damage by a toxin. This can also be defined as a clinical syndrome characterized by papillomacular bundle damage, central or cecocentral scotoma, and reduced color vision[1]. Data on the frequency of linezolid-associated optic neuropathy are still relatively limited and rather inconclusive. Two recent meta-analyses have reported significantly higher prevalence at 13.2% (10/76 patients) in 2012 and 8% 923/246) in 2015[3] .

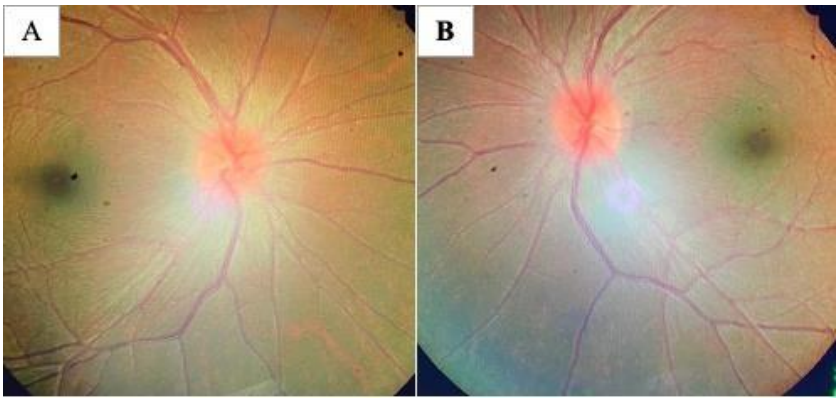
Among many causes of TON, one of the substance that can induce TON are antibiotic such as Linezolid[4]. In the most recent treatment guidelines by the World Health Organization (WHO) linezolid is recommended as a core second-line drug in the Multidrug-resistant tuberculosis (MDR-TB) regimen. Long term of linezolid treatment can trigger or enhance Linezolid induced toxic optic neuropathy (LION). The aim of this study are to identify the ocular manifestation, proper management and follow up of Linezolid induced optic neuropathy (LION) as the side effect of Linezolid in MDR-TB therapy

CASE PRESENTATION

A 48 years old woman referred from Pulmonology department with blurred vision of both eye since 7 days before. Blurred vision appeared slowly and were more severe in the left eye. Eye movement pain, double vision, headache, nausea and vomiting were

denied. The patient has been diagnosed with multidrug resistant tuberculosis of lung since May 2022 and has been consuming antituberculosis therapy (ATT) for 8 months (start from May 18th 2022). The Regiment were BDQ 400 mg, LFX 750mg, CFZ 100 mg, LZD 450 mg, CS 500 mg and B6 Vitamin100 mg. Patient also complaining of tingling sensation of both lower extremity 3 months before. There were no history of hypertension, diabetes, and trauma. History of spectacles (-2.75 on right eye and -2.50 on left eye) since 10 years ago but patient didn't feel comfortable wearing the spectacle.

In examination, the Visual acuity were 3 meter counting finger and 2 meter counting finger in left eye. Ishihara color vision in right eye were 4/38 plates, and 2/38 plates in left eye. The ocular movement and confrontation test was within normal limit. The examination of cranial nerve was within normal limit. Anterior segment examination was within normal limit. There was no relative afferent pupillary defect (RAPD). From Funduscopic examination there were hyperemic optic disc with blurred border in both eyes without elevasion. There weren't any paton's line or obscuration of vessel **(Figure 1).** Visual field examination with The Humphrey Perimetry (HFA) shows central scotoma in both eyes **(Figure 2)**. From the Optical Coherence Tomography (OCT) revealed increased of Retinal Nerve Fiber Layer (RNFL) thicknes, Inner limiting Membrane – Retinal Pigment Epithelium (ILM-RPE) thickness and Ganglion Cell–Inner Plexiform Layer (GCL-IPL) thickness in all quadrant **(Figure 3)**.



. **Figure 1**. Funduscopic Examination from A) Right Eye and B) Left Eye shows there were hyperemic with blurred margin of optic disc in both eyes (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo)

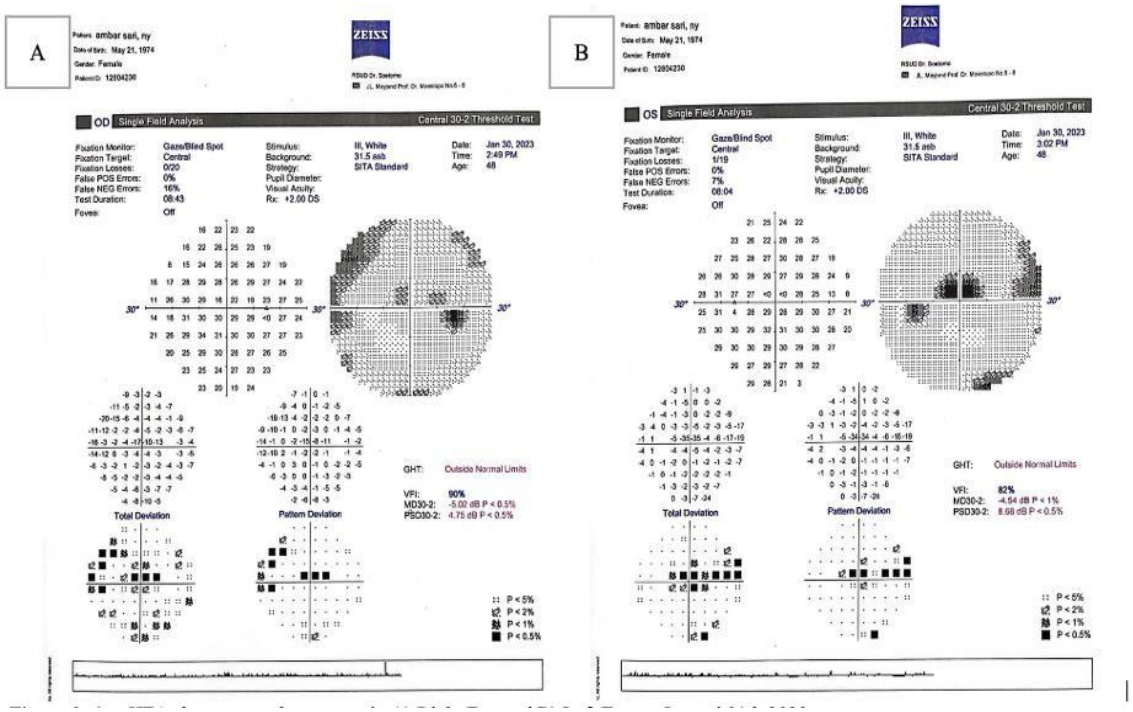


Figure 2. HFA shows central scotomas in A) Right Eye and B) Left Eye on Januari 31th 2023 (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo)

the examination in May 22th 2022 on the baseline examination before given the ATT, there were no ophatlmology complain. The best visual acuity was 5/7.5 in the right eye, and 5/5 in the left eye. Ishihara colour vision test was 38/38 plates in both eye. Eye movement of both eye within normal limit without any pain. Anterior segment were within normal limit, with no relative afferent pupillary defect. Funduscopic examination were within normal limit **(Figure 4).** HFA examination shows no visual field defect **(Figure 5)** and Optical Coherence Tomography is within normal limit on the RNFL thickness **(Figure 6).**

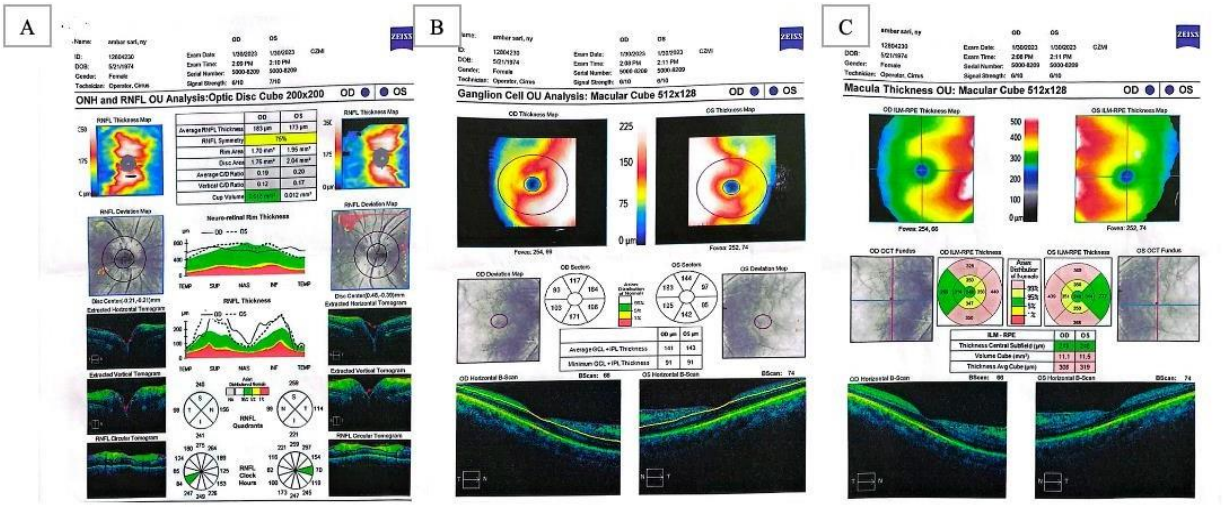


Figure 3. OCT from the both eyes shows thickening of A) RNFL, B) ILM-RPE and C) GCL-IPL thickness on Januari 31th 2023 (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo)

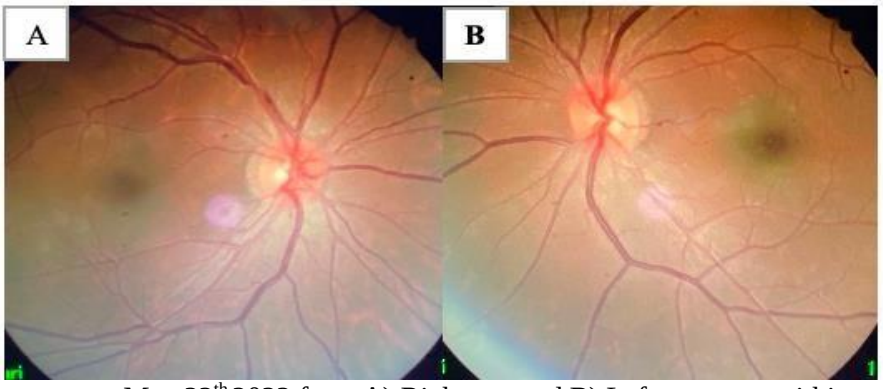


Figure 4. Posterior segment on May 22th 2022 from A) Right eye and B) Left eye were within normal limit. (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo)

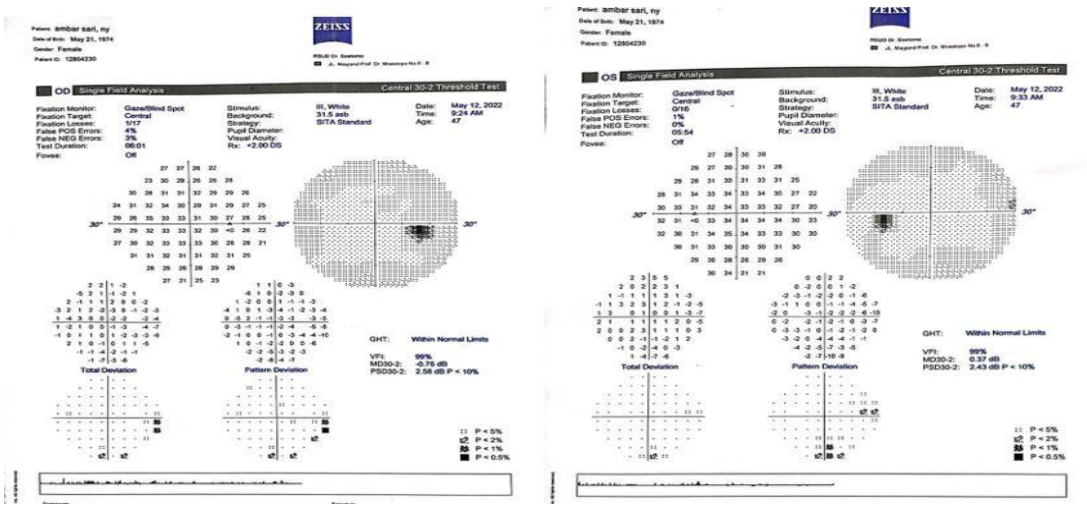


Figure 5. HFA on May 22th 2022 from the A) Right Eye and B) Left Eye were within normal limit (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo)

Linezolid-induced optic neuropathy was initially suspected and oral linezolid was discontinued from February 1st and replaced with Delamanid 2x00 mg after consultation with pulmonology depatement. Patient treated with oral methylprednisolone 16 mg two times for a day five days, neurotropic once a day, and folic acid once a day. Patient came on August 1st 2023 at the 6 months after replacement of Linezolid as the TB -MDR regimen with no complain of visual loss. Segemnt anterior within normal limit with a minimal opacities in lens of both eyes. Visual acuity examination revealed 5/30 with correction S-2.50 C-1.25 A90 became 5/5 in right eye and 5/20 with correction S-1.50 C-0.25 A 90 became 5/6.5 in left eye. The Ishihara test is 35/38 on both eyes.

Funduscopic examination revealed normal fundus, without any sign on hyperemic optic disc **(Figure 7)**. The visual field test with Humphrey Perimetry shows no visual field defect **(Figure 8).** Optical Computed Tomography revealed no RNFL thinckening in both eye with thining of superior quadrant in both eye. From GCL IPL revealed thinning in inferior quadrant of both eye **(Figure 9)**. From the follow up examination revealed improvement of visual acuity, color perception, visual field and RNFL thickness in both eye after 6 months LZD was stopped and replaced with another regimen of MDR-TB therapy.

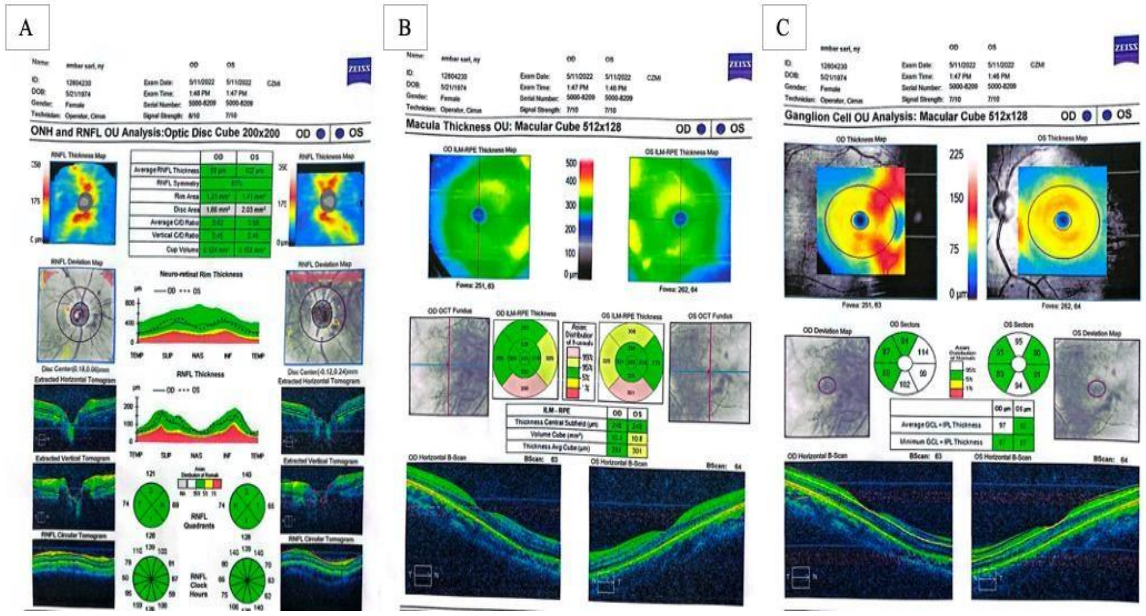


Figure 6. OCT on May 22th 2022 from the both eye were within normal limit. (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo).

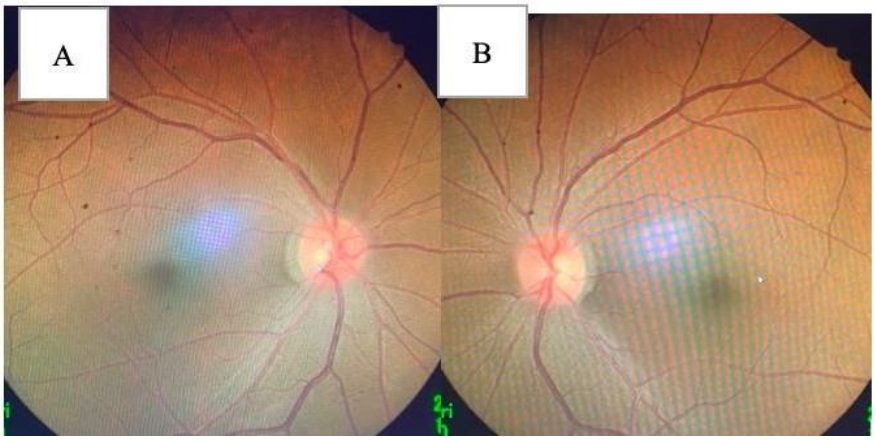


Figure 7. Funduscopic examination in August 1st 2023 revealed A) Right eye and B) Left eye within normal limit without any sign of disc edema (Picture taken with patient's
consent. Courtesy: Poli Mata RSUD Dr. Soetomo).

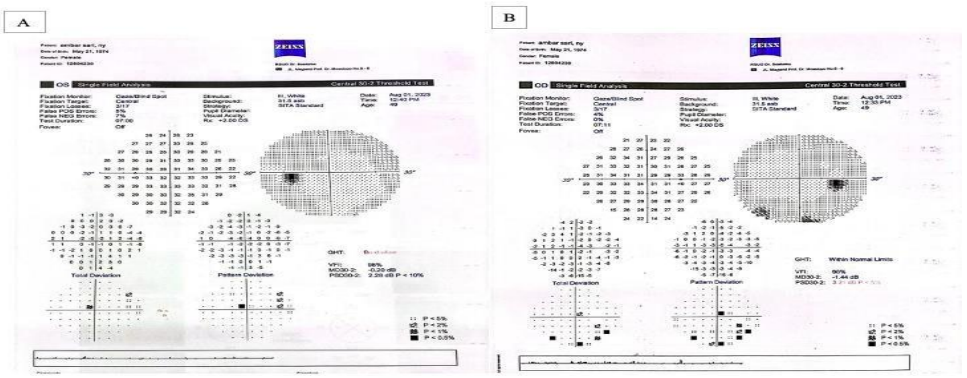


Figure 8. HFA on on August 1st 2023 shows within normal limit, no sign of central scotoma in A) Right eye and B) Left eye (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo)

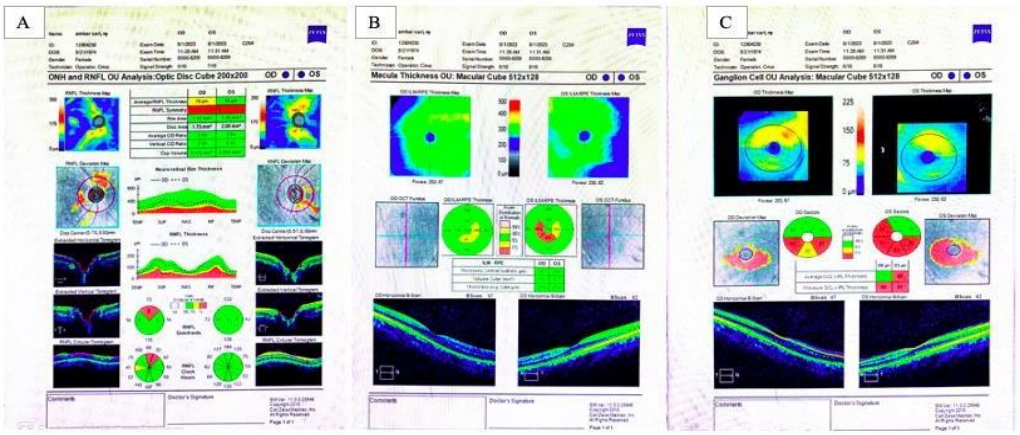
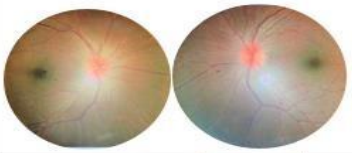
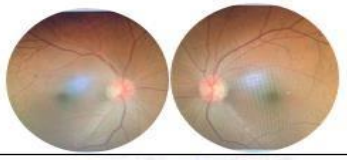
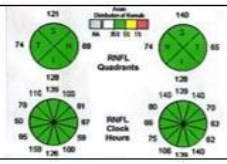
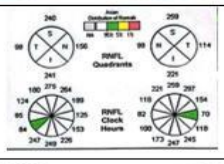
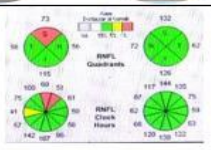
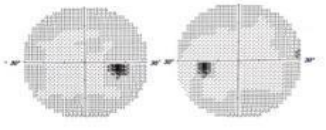
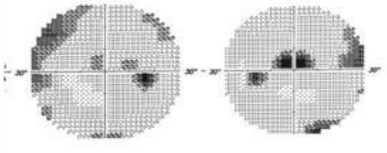
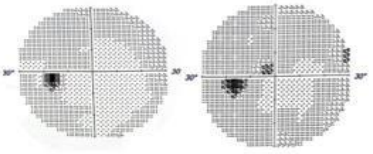


Figure 9. OCT on August 1st 2023 revealed improvement of A) RNFL,B) ILM RPE and C) GCL IPL thicknes compared to the last visit, there is no sign of bilateral disc edema (Picture taken with patient's consent. Courtesy: Poli Mata RSUD Dr. Soetomo).

The following table is the follow-up examination of the patient from the first visit until 6 months discontinuation of ATT **(Table 1).**

Table 1. Follow-up examination of the patient from the first visit until 6 months discontinuation of ATT

	May 22th 2022 (Baseline)	**January 30th 2023 (first visit)**	**August 1st 2023 (6 month after Linezolid stopped)**
Best Corrected Visual Acuity	VOD : 4/60 CC S-2.50 C-1.00 A76 → 5/7.5 VOS : 5/15 CC S-0.75 C-0.50 A100 → 5/5 Ishihara OD : 38/38, OS 38/38	VOD : 2/60 VOS : 3/60 Ishihara OD :4/38, OS : 2/38	VOD : 6/30 CC S-2.50 C-1.25 A90 → 5/5 VOS : 6/20 CC -1.50 C-0.25 A90 → 5/5 Ishihara : OD : 35/38 , OS ; 35/38
Funduscopic examination			
OCT			
HFA			

DISCUSSION

Toxic optic neuropathy (TON) is a group of medical disorders which can be defined by visual impairment due to optic nerve damage by a toxin. This can also be defined as a clinical syndrome characterized by papillomacular bundle damage, central or cecocentral scotoma, and reduced color vision[1]. Although these problems have been classified as optic neuropathies, in many of these entities, the primary lesion has not actually been localized to the optic nerve and may possibly originate in the retina, chiasm, or even the optic tracts. TON has multiple causes with multiple signs and symptoms. Both toxic and nutritional factors play a synergistic role in several of these disorders. [1] The Clinical feature of TON have various signs and symptoms[2] **(Table 2).**

Table 2. Clinical Feature of toxic optic neuropathy[2]

Symptom
Diminution of vision: bilaterally symmetrical, painless, gradually Progressive
Dyschromatopsia
Signs
Centrocecal field defects
Pupils: sluggish, no RAPD
Optic disc: normal, swollen, or hyperemic in early stages, Absence of temporal optic disc pallor later

Some risk factor of toxic optic neuropathy are nutritional deficits, including the vitamins thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), cobalamin (B12), folic acid, and proteins with sulfur-containing amino acids that can trigger or enhance toxic optic neuropathy**.** The use of systemic medications in high doses or for a prolonged duration might also cause toxic optic neuropathy**.** And other factor such as exposure to a toxic substance in the environment, Patients with decreased renal function or liver disease are at risk with certain substances[1.3] Optic neuropathy may result from exposure to a neuropoisonous substances toxin in the environment, ingestion of certain foods or other materials containing toxic substances, or from elevated serum drug levels. Among the many causes of TON, common ones include: ingestion of methanol (wood alcohol), treatment with disulfiram for chronic alcoholism, halogenated hydroquinolones (amebicidal medications), Isoniazid, ethambutol, streptomycin (tuberculosis treatment), Digitalis, amiodarone (Antiarrhythmic agent), antibiotics such as linezolid and chloramphenicol and cimetidine and also antimalaria such as Chloroquine, quinine. Medication of cancer such as vincristine, and cyclosporine. Tobacco is also an important cause of TON [4]. One of the substance that can induce TON are antibiotic such as Linezolid[2]. In the most recent treatment guidelines by the World Health Organization (WHO) linezolid is recommended as a core second-line drug in the Multidrug-resistant tuberculosis (MDR-TB) regimen. Long term of linezolid treatment can trigger or enhance Linezolid induced toxic optic neuropathy (LION). Data on the frequency of linezolid-associated optic neuropathy are still relatively limited and rather inconclusive. Two recent meta-analyses have reported significantly higher prevalence at 13.2% (10/76 patients) in 2012 and 8% 923/246) in 2015[10].

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis that is resistant to at least two anti-tuberculosis drugs (ATT), isoniazid and rifampicin and other first-line anti-TB drugs such as ethambutol, pyrazinamide and streptomycin. MDR TB criteria consisted of TB patients who failed treatment in category two, TB patients who were treated in category two who were not converted after three months of treatment, TB patients with a history of non-standard TB treatment and used fluoroquinolones and second-line injection drugs for at least one month, TB patients who failed treatment. first category, first category TB patients who are not converted, first or second category relapse case TB patients, TB patients who return after loss to follow-up, TB suspects who have a history of close contact with MDR TB patients, TB-HIV co-infected patients who do not respond clinically or bacteriologically four to giving ATT, TB with Acquired Immunodeficiency Syndrome (AIDS), TB in pregnancy, children, diabetes mellitus, malnutrition, immune system disorders, new case bacteriological TB, TB with a history of previous treatment with negative smear and Extrapulmonary TB[6]. The grouping of MDR TB drugs currently used in Indonesia are divided into three groups, group A the fluoroquinolone class, levofloxacin and moxifloxacin, bedaquiline and linezolid are considered very effective and highly recommended as a regimen unless there are contraindications, group B, namely clofazimine and cycloserine or terizidone are recommended with conditions as agents of second choice, group C drugs used when group A and B drugs cannot be used. Drugs in group C are ethambutol, delamanid, pyrazinamide, imipenem-

cilastatin, meropenem, amikacin, streptomycin, ethionamide or prothionamide and para-amino salicylic acid[6]. In this case, patient was diagnose with TB MDR since May 2023 and prescribed Group A invidual drug regimen for TB MDR which is Bedaquiline 400 mg, Levofloxacine 750mg, Clofazimine 100 mg, Linezolid 450 mg, Cyclocerine 500 mg and B6 Vitamine 100 mg from Pulmonolgy Departement for 18 months due to resistancy of Fluoroquinolone.One of the drug regiment, Linezolid represents the first member of the synthetic oxazolidinone group of antimicrobials designed to treat MRSA and vancomycin-resistant Enterococcus. Linezolid has been shown to be effective in the treatment of MDR-TB and XDR-TB. However, several studies have found side effects and toxicities, primarily bone marrow suppression and peripheral and optic neuropathy, to be limiting factors in the use of linezolid[7] .

Linezolid induced toxic optic neuropathies (LION) are characterized by slowly progressive, symmetric, and painless vision loss. Some patients may initially only observe dyschromatopsia. As visual acuity decreases, a protan defect first develops. Because of the symmetric and bilateral visual impairment, a relative afferent pupillary defect is often not present. The pupillary light response may be bilaterally sluggish or absent. The pupils are often dilated in completely or nearly blind patient.The optic disc may be normal or mildly hyperemic with temporal optic disc pallor in the early stages. Peripapillary splinter hemorrhages may occasionally be seen. After a period of several months to years, PMB atrophy and temporal optic disc pallor are followed by diffuse optic atrophy. Disc edema and hyperemia are seen more often in acute intoxications such as methanol or ethylene glycol poisoning. The severity and course of development of PMB and temporal disc atrophy varies according to the type of toxin.Visual field evaluation, static (HFA) or kinetic (Goldman), is absolutely essential in the evaluation of any patient suspected of having toxic/nutritional optic neuropathy. Various pattern of visual field defects for optic neurophaty such as Cecocentral scotoma,paracentral, Arcuate scotoma, Broad arcuate, and Nasal arcuate [20] . Central or cecocentral scotoma with preservation of the peripheral field are characteristic of toxic optic neuropathies and are actually most prevalent in patients with these disorders. Rarely, patients may present with other defects. The field defects tend to be relatively symmetric. This patient shows acute onset of bilateral gradually visual loss, with bilateral optic disc edema with history of linezolid medication for more than 28 day (400mg once a day). The HFA examination shows bilateral central scotoma with thickening of RNFL thickness of both right eye and left eye. that the diagnosis of LION is more likely than other optic neuropathy.

LION is postulated to be a drug related mitochondrial optic neuropathy (MON). Retinal ganglion cells (RGCs) contribute axons, which travel together in the retinal nerve fibre layer towards the optic nerve. These axons are rich in mitochondria, especially in the unmyelinated intraocular and prelaminar region (and in the postlaminar region at the nodes of Ranvier); these have been interpreted as sites with high energy demands[9]. These axons are myelinated by oligodendroglia posterior to the lamina cribrosa, and thereby enjoy the efficiency of salutatory conduction[10,11,12]. . It has been hypothesized that optic and peripheral neuropathy may potentially be the result of this mitochondrial dysfunction[8], Mitochondria, through their respiratory chain, are the major source of cellular reactive oxygen species (ROS) as a product of ATP synthesis. The disruption of oxidative phosphorylation at any step in the respiratory chain leads to considerable energy depletion coupled with the accumulation of ROS in the RGCs. This accumulation of ROS lowers the electrical potential across the mitochondrial membrane and this opens the mitochondrial permeability transition pores, which acts as an apoptotic switch by releasing factors promoting cell death such as cytochrome *c*. This mitochondrial dysfunction may also trigger compensating increases in mitochondria, manifesting on OCT as retinal nerve fibre oedema leading to visual loss [13,14]. Linezolid is generally well tolerated when consumed less than 28 days. Both optic and peripheral neuropathies have been reported in patients taking linezolid for longer periods[15,16]. Toxicity has been associated with off label extended therapy of 5–10 months[17] . The linezolid minimum inhibitory concentration (MIC) reported by the pharmaceutical company (Pfizer) for *M. tuberculosis* is 1 µg/mL. A cumulative weekly target area under the curve (AUC) of 350–700 µg×h/mL On the basis of these data, it is concluded that linezolid at a dosage of 600 mg once daily should be effective, with less toxicity[18]. In this case, patient was already consumed linezolid 450 mg once a day as one of the regimen of ATT for 8 months. Majority of the patients with optic nerve damage improve when the drug is stopped which possibly could be because the inciting factor is withdrawn before apoptosis begins and permanent axonal loss ensues[19].

The first step in managing Linezolid induced toxic optic neuropathy, as with any toxic process, is to remove the causative agent. This may cause some reversal of the process. Treatment of Toxic Optic Neuropathy is dictated by the cause of the disorder. Medical therapy includes vitamin supplementation which is needed in many patients with toxic neuropathy such as vitamin B6 at a dosage of 50–100 mg daily. The efficacy of corticosteroid treatment is a controversial matter. A study observed clinical improvement, both in patients treated with corticosteroids and in those not treated.

In other study, corticosteroid administration was beneficial in two cases while three experienced a worsening in their neuropathy[22]. Therefore, more studies are necessary, on a wider population, in order to reach final conclusions about the benefit of corticosteroids. Patients with toxic/nutritional optic neuropathy should be observed initially every 4–6 weeks and then, depending on their recovery, every 6–12 months. The patient's visual acuity, pupils, optic nerves, color vision, and visual fields should be assessed at each visit. Vision gradually recovers to normal over several weeks, though it may take months for full restoration and there is always the risk of permanent residual vision deficit. In this case, patient were diagnosed with Linezolid induced toxic optic neuropathy and Linezolid were stopped and given Neurotropic supplement.

Linezolid-induced optic neuropathy (LION) is nearly reversible, but the exact duration of symptom resolution following drug discontinuation is unknown. The majority of reported cases of optic neuropathy resolved within 1–3 months of drug discontinuation. However, the presence of other systemic illnesses can impede optic neuropathy recovery. Visual acuity usually recovers before color vision. Morbidity of these disorders depends on the risk factors, the underlying etiology, and the duration of symptoms before the institution of treatment[22,,23,24]. However, the presence of other systemic illnesses can impede optic neuropathy recovery[25]. Full visual recovery has been reported in some cases after discontinuing the drug. However, the peripheral neuropathy is often irreversible. Improvement in symptoms after the discontinuation of the drug further strengthened the diagnosis of drug-induced toxic neuropathy[15]

A patient with advanced optic atrophy is less likely to recover visual function than a patient who does not have such pathologic changes. The prognosis is variable and depends upon the nature of the agent, total exposure prior to removal, and degree of vision loss at the time of diagnosis [4].In this case, patient shows visual improvement in 6 months after discontinuation of Linezolid therapy. Funduscopic examination, OCT and HFA shows no thickening RNFL thickness and no visual field defect. For patient with medication of Linezolid without any side effect, patients should be closely monitored for signs or symptoms of bone marrow toxicity and peripheral and optic neuropathy. Bone marrow toxicity can be monitored with a complete blood count measured before starting and monthly throughout treatment, and neuropathy can be monitored by a monthly examination. Both should be complemented by patient education about side effects. Patients should be closely monitored within 1 month after initiating linezolid, followed by a subsequent evaluation every 30–60 days beginning 3 months from initiation[26]. Patients should also be cautioned to report any adverse side effects while receiving linezolid, especially visual changes or sudden loss of vision. Vitamin B6 should be coadministered with linezolid as a neurotropic agents.

CONCLUSSION

Linezolid induced toxic optic neuropathy (LION) is a complication associated with the prolonged use of linezolid, regardless of the dose received, and reversible in most cases. The increasing use of linezolid in regimens for treatment of multi-drug resistant tuberculosis has led to an increase in the incidence of toxic optic neuropathy associated with the prolonged use of linezolid. Therefore, it is important to conduct multidisciplinary follow-up for patients on long treatment regimens more than 28 days, particularly in those with visual alterations. Ophthalmologists and physicians must be aware that monitoring of visual function is important in patients on long-term linezolid therapy and that early recognition of toxicity and discontinuation of drug results in complete visual recovery.

DECLARATIONS

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Competing Interests

The authors have no competing interests to declare.

Ethical Approval

The study was approved by the appropriate ethics committee and conducted according to relevant guidelines and regulations.

Informed Consent

Not applicable.

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