Outcome of Linezolid induced optic and peripheral neuropathy in a Pakistani patient treated for multidrug-resistant pulmonary tuberculosis: A Case report

Ahmad Nawaz (ahmad_nawaz3534@yahoo.com)
king edward medical university

Case Report

Keywords: drug-resistant tuberculosis, Linezolid, optic neuropathy, peripheral neuropathy

Posted Date: March 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1478191/v2

Abstract

Linezolid is a core second-line drug used for the treatment of extensively and multidrug-resistant tuberculosis. Linezolid showed the promised efficacy in the treatment of drugs resistant tuberculosis. However, the associated adverse effects such as optic and peripheral neuropathy are the major obstacles for its long-term therapy. We recently encountered a case of progressive deterioration of vision and numbness in the feet in a 32-years-old male undergoing linezolid therapy for 12 months for multidrug-resistant tuberculosis. Nerve conduction studies were highly suggestive of sensory polyneuropathy while the fundoscopic image was highly favorable of optic neuropathy. A slight improvement was seen in vision with no improvement or worsening of peripheral neuropathy on follow-up visits after the discontinuation of linezolid. In a developing country like Pakistan, whereas the management of developing resistance to tuberculosis is a major problem, awareness among physicians for close follow-up of a patient using long-term linezolid therapy should be created to avoid such serious optic and peripheral neuropathy.

Introduction

Tuberculosis is one of the infectious diseases that has proven fatal throughout the globe because of its multisystemic involvement leading to a grave prognosis. The emergence of the resistance to the first-line anti-tuberculous therapy is not uncommon in economically developing countries. So, the second-line anti-tuberculosis agents are utilized frequently for the treatment of extensively or multidrug-resistant tuberculosis (1). Linezolid, a synthetic oxazolidinone has been one of the alternative second-line options against the drugs resistant to mycobacterium tuberculosis owing to its promised efficacy (2). However, the medically unexpected serious unfavorable effects such as myelosuppression, optic, and peripheral sensory neuropathies have become the basis of close follow-up to early identify these undue effects and discontinuation of linezolid to avoid these irreversible consequences (3,4). Recently, we encountered a case of a 32-years-old male being treated with the linezolid-based regime for multidrug-resistant tuberculosis admitted with the chief complaint of progressive deterioration of vision and symptoms of peripheral neuropathy. The identification of that culprit drug and its cessation results in the mild improvement of visual acuity and color perception.

Case Presentation

A 32-years-old Pakistani male normotensive normoglycemic was admitted to the neurology department of a tertiary care hospital with a four months history of progressive numbness & severe tingling sensations that initially involved both hands and feet later on progressed & subsequently involved his legs up to knee and arms up to elbow within2-months. Initially, the patient was having no disturbances in gait but within 2-months he also started having difficulty in walking due to decreased sense of balance. The patient also complained of visual impairment from 4 months that was painless gradually worsened from the blurring of vision to fingers counting only. The patient was diagnosed case of multidrug-resistant tuberculosis and was on clofazimine, pyrazinamide, and linezolid for the last 12 months.

Linezolid was stared at a dose of 600 mg once daily by the drug-resistant tuberculosis management team of the Chest infection and tuberculosis department. The patient was a non-smoker, non-alcoholic, and was having normal bowel habits. On inquiry of dietary pattern, Patient used to take meat 2-3 times per week. Previously, He had no history of neuropathy, nephropathy, retinopathy, or macrovascular complications. There was no history of joints pain or any features favoring the autoimmune disease or vasculitis. The patient was not using any medications other than that of a linezolid-based regime for MDR-tuberculosis. Patient-reported no exposure to chemicals and none of the closed family members suffered from peripheral neuropathy.

Physical Examination:

On general physical examination, the patient was afebrile with normal vital signs. Ophthalmological examination revealed a significant diminution of visual acuity in both eyes limited to only fingers counting. The patient was unable to perceive the red color from both eyes. Contrast sensitivity was also reduced in both eyes. However, the pupils were normal and equal in size and were reactive to light equally and bilaterally. Fundus evaluation showed bilaterally symmetrically edematous discs. Neurological examination of the motor system revealed normal power (MRC scale) Grade 5/5 In all limbs proximally and distally. Examination of sensory sensations revealed reduced pinprick and fine touch sensations up to the knee and reduced joint position sense in lower limbs. Sensory system examination of the upper limb was unremarkable. The cerebellar examination was also unremarkable. The speech was fluent with normal comprehension and repetition. The gait of the patient was a broad-based ataxic gait with positive Romberg's sign.

Investigations:

Complete blood picture showing normocytic normochromic anemia while Thyroid profile, serum Ferritin level, serum vitamin B12 level, HaemoglobinA1c level, Antineutrophilic antibodies levels by ELISA method and protein electrophoresis results summarized in Table 1. Cerebrospinal fluid analysis showed a minimal increase of protein level at 52 mg/dl with normal CSF white blood cell counts and cerebrospinal glucose level. The cerebrospinal fluid's opening pressure was $15cm^2H_20$. Nerve conduction studies showed a marked reduction in amplitude of sensory nerves of lower limbs as compared to upper limbs. Nerve conduction study findings were suggestive of length-dependent axonal sensory polyneuropathy. Optical coherence tomography image of optic nerve head shown increased thickened of Retinal nerve fiber layers (Normal 220+20) of 320um &330 in Right and left eye respectively. Fundoscopic images showed bilateral optic disc edema (Figure 1). Visual field test done by visual field analyzers machine showed bilateral central scotoma (Figure 2). Magnetic resonance imaging of the brain and optic nerve was unremarkable.

Differential Diagnosis:

Based on clinical history and examination, our provisional diagnosis was metabolic neuropathy with optic chiasmatic arachnoiditis. All the possible reversible causes of metabolic neuropathy were ruled out

by the relevant investigations. Radiological images of the brain and orbit showed no evidence of optic chiasmatic arachnoiditis. So, our final diagnosis was made of Drug-induced toxicity as no literature was suggestive of clofazimine or pyrazinamide-induced neuropathy that led to our final diagnosis of linezolid induced optic and peripheral neuropathy.

Treatment:

The culprit drug linezolid was immediately withdrawn from the treatment regime. However, Pyrazinamide along with clofazimine continued after the consultation from Chest-infection and Tuberculosis ward. Gabapentin was given initially 75 mg once daily then 100 mg twice a day for 12 weeks for neuropathic symptoms.

Outcome and follow-up: After the diagnosis, the patient was discharged with the addition of gabapentin to his medical treatment for 12 weeks. The patient was called up for follow-up after 12 weeks. The assessment was made based on clinical symptoms. His visual acuity was improved to 20/50 in both eyes. His fundoscopic examination also revealed a mild improvement in disc swelling. But the sensation of pinprick and proprioception in lower limbs was not improved. His gate was still ataxic. No further worsening was seen on sensory system examination. His sputum smear for AFB become negative after 2-months of further treatment with clofazimine and pyrazinamide.

Discussion

In a developing country like Pakistan where Tuberculosis is still a major stumbling block due to lack of awareness and poor economic status which leads to unnecessary delay in the early diagnosis of tuberculosis and development of resistance to first-line therapy. In this clinical scenario, the use of second-line agents like linezolid has been the frequent choice for multidrug-resistant tuberculosis (1). Linezolid, the first brand-new synthetic oxazolidinones has a broad spectrum of antimicrobial activity not only against the Methicillin and vancomycin-resistant staph aureus but also effective for the first-line drugs resistant mycobacterium tuberculosis as well (5). Based on the systemic review from the literature, it is evident that linezolid showed a success rate of more than 80% for the Multidrug- mycobacterium tuberculosis (6).

Here, we demonstrated a diagnosed case of multidrug-resistant tuberculosis who was on the linezolid-based regime presented with optic disc and peripheral neuropathy. In our case, there was no previous history of any chronic ailment or agent causing this subacute onset of neuropathic symptoms. Furthermore, the clinical signs on the bedside, fundoscopic images, normal laboratory results for the possible causes of neuropathy, and nerve conduction study findings suggestive of axonal type sensory polyneuropathy established the pathway of our diagnosis.

A systemic review and meta-analysis of 23 studies which was carried out in 14 countries suggested a cumulative proportion of 29.92% for neuropathy in patients of drug-resistant tuberculosis treated with linezolid (7). Another retrospective study of 16 patients diagnosed with MDR-tuberculosis who were on a

linezolid-based regime revealed the development of peripheral neuropathy in 7 patients with or without optic neuropathy. This study also demonstrated the resolution of symptoms of optic neuropathy only in one patient on the discontinuation of linezolid. But no improvement was seen in their sensory complaints in any of the 16 patients enrolled (8). Ritesh Kumar shah also reported a case of optic neuropathy in a 28-year-old female who received oral linezolid of 600 mg dose once daily for 14 months developed bilateral optic disc neuropathy. In this patient, symptoms of optic neuropathy also become reversible on the cessation of the linezolid therapy (9). These studies did not give information about the duration of exposure before the development of toxicity and improvement in optic neuropathy after the discontinuation of linezolid. In our study, the patient received linezolid-based therapy for 12 months preceding the manifestation of the symptoms. As the patient reported to us after a long period of drug exposure, therefore, the only mild clinical improvement was seen in the features of optic neuropathy and no improvement or worsening was observed in the sensory complaints. Another clinical trial was conducted on 796 patients who were receiving linezolid for highly resistant gram-positive microbes. This article concluded that the incidence of peripheral neuropathy was 32.9% in the patients who used linezolid for more than 28 days in comparison to it was reported less than 1% who continued linezolid for 28 or fewer days. The safety of linezolid in terms of neuropathy for more than 28 days has not been evaluated in this clinical controlled trial (10).

Linezolid binds with 70S ribosomal initial complex resulting in the inhibition of protein synthesis in bacteria. 70S ribosomal initial complex is not present in mammalian cells (11).

In addition to the neuropathic symptoms, long-term use of linezolid is also associated with myelosuppression. Though the exact underlying mechanism of its toxicity is still unclear it has been shown that it reduces the mitochondrial respiratory chain activity ultimately resulting in hematological complications and neurological consequences (12). Previously it was common to know the only isoniazid induced peripheral neuropathy which can be prevented by the use of pyridoxine along with it and is usually reversible on the cessation of isoniazid as compared to linezolid induced neuropathy which is almost irreversible. While ethambutol and linezolid both cause optic neuropathy and, in both cases, early cessation of drugs results in complete resolution of optic neuropathy (13).

There are certain limitations that the authors would like to acknowledge. Owing to limited resources the electrophysiological studies and optical coherence tomography on follow-up visits could not be done. However, after identifying the causative drug and its discontinuation therapy, careful clinical assessment was done on every follow-up visit to monitor the worsening or improvement in symptoms. Although the patient presented with symptoms belatedly, early identification results in improvement of visual symptoms. Hence the educational value of our case for practicing physicians and ophthalmologists is paramount in sense to highlight the need of arranging close follow-up sessions of patients receiving long-term therapy of linezolid.

Conclusion

We reported an extremely diagnostically challenging case of drug-induced optic and peripheral neuropathy. The classic clinical signs and symptoms of optic disc swelling and peripheral neuropathy have largely fallen out of favor that can be seen in most cases of prolonged therapy of linezolid. The physicians need to monitor and recognize such symptoms clinically to stop the toxic drug early to prevent irreversible optic and peripheral neuropathy.

Declarations

Our manuscript fulfils all the criteria of the journal and complies with the requirements mentioned in the ‘Guide for Authors’. Consent was obtained from the patient for reporting of this case for educational purposes, and all principles of medical ethics were upheld. This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. All the authors have contributed significantly and are in agreement with the content of the manuscript.

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Tables

Table 1 is in the supplementary files section.

Figures

Figure 1

showing optic disc oedema of right and left eye

Figure 2

Visual field showing central scotoma in Right and left eye

Supplementary Files

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- Table1.docx