Profound vision loss: an investigation into linezolid toxicity

Extended linezolid use for resistant infections has been implemented in medicine. We present an investigation of linezolid-induced toxic optic neuropathy presenting with a significant decrease in visual acuity, dim vision, and loss of color discrimination.

1) Case History
   a) Patient demographics: 77 year old Caucasian man
   b) Chief Complaint: persistent, progressive, painless vision loss of both eyes, left eye worse than right. This has developed over 3 weeks. The visual acuity is considered blurred at distance and near, and now this professional writer is unable to read print. The vision is also considered to be dim bilaterally.
   c) Ocular history: myopia OU, presbyopia OU, posterior vitreous detachment OU, pseudophakia OU status post extra-capsular cataract extraction OU, glaucoma suspicion OU
   d) Medical history: depression, obstructive sleep apnea, chronic obstructive pulmonary disease, atrial fibrillation, gastro-esophageal reflux disease, osteoarthritis, onychomycosis, prostate cancer, vitamin D deficiency, obesity, benign essential hypertension, diverticulitis, chondromalacia patellae, prosthetic knee infection which cultured vancomycin-resistant enterococcus
   e) Medications: doxycycline, fluconazole, linezolid, warfarin, morphine, lorazepam, terazosin, diltiazem, omeprazole, budesonide/formoterol inhaler, cholecalciferol, ascorbic acid

2) Pertinent findings
   a) Clinical:
      i) BCVA: OD 20/80+1, OS 20/150-1
      ii) Pupils equal, round OU, reactive 4+ OD, 2+ OS, 1.5 log APD OS
      iii) Peripheral confrontation visual fields: full to finger count OD and OS
      iv) HRR color plates: 0/6 plates OD and OS with inability to identify test plates
      v) IOP: 14 OD, 15 OS
      vi) Optic Nerves: OD 0.45v/0.40h cup, trace inferotemporal pallor, rim otherwise intact; OS 0.85v/0.75h cup, 2+ diffuse pallor, diffuse rim erosion, extensive peripapillary atrophy
      vii) Severe retinal arteriolar attenuation OS
      viii) Humphrey 30-2 Visual Field
         (1) OD: Low patient reliability with high fixation loss (8/14), 25% false positives, and 23% false negatives. Mean deviation of -5.33 DB and pattern standard deviation of 3.84 DB.
pattern deviation reveals a mild superior arcuate vs lid/lens edge artifact and a superior paracentral depression.

(2) OS: Low patient reliability with gaze tracker revealing multiple lid closures for extended periods of time throughout the test. Fixation losses were 2/14, false positives 9%, and false negatives N/A. Mean deviation of -29.73 DB and pattern standard deviation of 3.31 DB. Pattern deviation reveals a central/paracentral depression/scotoma denser inferior.

ix) Optical coherence tomography
   (1) Retinal nerve fiber layer
      (a) OD: Average RNFL thickness: 96 microns, no obvious RNFL loss 360 and all quadrants within normal limits for age.
      (b) OS: Average RNFL thickness: 70 microns, significant RNFL thinning superotemporally and inferotemporally with diffuse loss of neuro-retinal rim

b) Physical:
   i) Patient denies headaches, proximal muscle aches, fever, jaw claudication, temporal/scalp tenderness, malaise
   ii) Unintentional loss of 10 lbs 3 months ago, but has since regained the weight
   iii) Patient has had recurrent infections of prosthetic knee joint, for which he is prophylactically taking oral doxycycline, fluconazole, and linezolid. Linezolid has been dosed at 600mg PO BID for the past year.

c) Laboratory studies
   i) Normal
      (1) WBC: 4.95 K/cmm
   ii) Abnormal
      (1) RBC: 3.41 M/cmm (L)
      (2) HGB: 10.9 g/dL (L)
      (3) HCT: 33.5% (L)
      (4) PLT: 120 K/cmm (L)
      (5) CRP: 19.7 mg/L (H)
      (6) ESR: 22 mm/hr (H)

d) Radiology studies
   i) Magnetic resonance imaging: No contributory pathology, although the patient has a non-specific enlargement of the pituitary gland. There is no compression of the visual pathway.

3) Differential diagnoses
   a) Leading/primary: Toxic optic neuropathy secondary to extended use of linezolid and open angle glaucoma
   b) Others: infiltrative optic neuropathies (inflammatory, neoplastic,
4) Diagnosis and discussion: After thorough examination and extensive testing, it has been determined that the most likely etiology of the optic neuropathy is linezolid toxicity in the setting of probable glaucomatous neuropathy of the left eye. With the normal MRI and relatively non-contributory serologic testing, the cause is unlikely to be inflammatory, infiltrative, metabolic, compressive, genetic, and/or paraneoplastic. Additionally, the patient has no family history of hereditary mitochondrial disease. Linezolid is an antibiotic within the oxazolidinone class that is designed to treat gram-positive bacteria that are resistant to other antibiotics. It is approved by the United States Food and Drug Administration for a maximum 28-day use; however, some clinicians have initiated off-label long-term use of linezolid \[^{1-3}\]. Extended use of linezolid has been shown to be associated with the development of toxic optic neuropathy. The etiology of the neuropathy is thought to be due to the antibiotic mechanism of action of linezolid. The drug acts on the 50s ribosomal subunit of the bacterial DNA, which is a subunit that is lacking in human DNA. However, human mitochondrial DNA more closely resembles the 50s subunit, thereby making the mitochondria more susceptible to damage from the antibiotic \[^{1-4}\]. Relying heavily on the energy produced by mitochondrial metabolism, the optic nerve and retinal ganglion cells, especially in the papillomacular bundle, can be negatively impacted through linezolid’s action \[^{1,2}\]. In the case of our patient, the most likely cause of his vision loss and optic neuropathy is his long-term use of linezolid. Although he has asymmetric glaucomatous damage to his left optic nerve, the clinical findings, lab studies, and radiological studies suggest that the most likely cause of the patient’s vision loss is linezolid-associated toxic optic neuropathy.

5) Treatments

a) The only known form of treatment for linezolid-associated optic neuropathy is cessation of the antibiotic \[^{4,5}\]. The presented patient stopped taking the medication after our initial evaluation, once we received approval from his orthopedist. Literature review has shown that in similar cases, some level of visual recovery can be expected after weeks to months post-cessation of linezolid \[^{5-8}\]. Due to apparent optic atrophy, visual prognosis is guarded; however, other cases have shown significant visual recovery after up to one year of extended use of linezolid \[^{3-5,7,8}\]. After one week, the presented patient’s vision is stable without evidence of worsening.

b) Literature review: We conducted a complete Medline search using linezolid and the MeSH term “optic nerve disease.” This search yielded 12 results pertinent to our case.
c) Reference list


6) Conclusion

a) Although complicated by glaucoma, the optic neuropathy experienced by our patient is most probably due to mitochondrial toxicity associated with his extended use of linezolid. As evidenced through other case reports and literature review, our patient’s best
potential for visual recovery lies in the cessation of the antibiotic, which is counterbalanced by the risk of resurgence of his infection. We will continue to monitor our patient’s visual progress through comprehensive examination with dilated fundus examination and necessary ancillary testing, including color vision testing, visual fields, and optical coherence tomography. In cases such as this, a thorough systemic review is essential to help uncover the etiology of complex ocular disease, which often may have more than one source of pathology. The available case reports and reviewed literature also verify a probable need for closer monitoring of patients who are using antibiotics or other medications with high risk for toxicity, especially when these medications are used for a prolonged period of time.