

Progressive Bilateral Visual Loss Due To Vincristine Induced Optic Neuropathy

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Abstract

Optic neuritis (ON) is an inflammation of the optic nerve that usually stems from demyelinating disorders such as multiple sclerosis (MS). It leads to subacute unilateral or bilateral vision loss accompanied with pain on eye movements. Certain drugs cause optic neuropathy due to toxicity to ganglion cells. Thorough history, clinical diagnosis with high degree of suspicion and immediate treatment with high-dose corticosteroids is the usual regimen followed for regain of visual acuity. Vincristine is a plant derived mitotic inhibitor used in the treatment of several cancers. While vincristine is generally well-tolerated, neurotoxicity is a known adverse effect, most commonly presenting as peripheral neuropathy. Optic neuropathy, especially bilateral, is exceedingly rare and poses a risk of irreversible blindness if not promptly identified. There are many reports of unilateral vincristine induced neuropathy in paediatric tumours or haematological cancers. This report discusses a patient with right fronto-temporal Glioblastoma Multiforme who developed bilateral optic neuropathy secondary to vincristine therapy.

Keywords: bilateral optic neuritis, chemotherapy, glioblastoma multiforme, optic neuropathy, vincristine

INTRODUCTION

Expansion of targeted therapy of cancers have given way to newer drugs showing ocular toxicity in recent times. Several synthetic molecules specified to act on particular receptors and enzymes have been linked to ocular surface side effects [1]. Few others are linked to cause optic nerve disorders which can have debilitating consequences for vision [2].

The most common drugs that are commonly known to cause optic neuropathy include ethambutol, isoniazid, linezolid, amiodarone and sildenafil [3]. Protocols for screening and evaluation of patients on therapy with common drugs toxic to the optic nerve have been well cemented in ophthalmological practice. There is still scope of improvement in developing high degree of suspicion while evaluating patients on chemotherapeutic regimens.

Platinum based agents like cisplatin [4] and carboplatin, taxanes like docetaxel, antimetabolites like methotrexate, 5-fluorouracil and vincristine have also been known to cause severe diminution of vision. The group of alkaloid plants used in the treatment of cancer are the vinca alkaloids. Vinca alkaloids are an extract from *Catharanthus roseus* commonly called pink periwinkle plant or vinca plants. It is a class of anti-mitotic agents and anti-microtubule alkaloids [5]; it blocks the beta-tubulin polymerization in dividing cell

which helps in treating the cancer growing cells. Vinca alkaloids are used for the treatment of various types of cancer therapy, they are given in combined form with other drugs as they did not show any side effect or any cross resistance to the drug molecules. Vincristine can be useful in the treating acute leukemia, neuroblastoma, Wilm's tumor and other

lymphomas [6]. Vincristine is one of the drugs in PCV (Procarbazine, Carmustine, and Vincristine) chemotherapy used for the treatment of brain tumors like glioblastoma multiforme [7]. It has some common side effect peripheral neuropathy, suppression of bone marrow activity, constipation, nausea and vomiting. VCR shows rare conditions of hematologic toxicity and severe cases with myelosuppression condition.

Though peripheral neuropathy is a commonly noted side effect of vincristine, optic neuropathy due to this alkaloid is reported sparsely. This case reports highlights the need for early screening and recognition of this adverse effect in patients undergoing PCV regimen.

Case Presentation

Our patient was a male in his late 40's who was started on 3 cycles of procarbazine, lomustine (CCNU) and vincristine [PCV] regimen for biopsy proven right frontal astrocytoma - NOS, WHO Grade 4. Three cycles of PCV were given over 7 month period. He initially presented with progressive blurring of vision in both eyes for one month following the 3rd cycle of chemotherapy. He had underwent right frontal craniotomy with microsurgical excision of space occupying lesion and re-craniotomy with radical excision of the lesion eight

months back for initial complaints of headache and seizures. Patient was planned for concurrent chemoradiation, in concurrence with tumor board, owing to its aggressive nature. He had also underwent external beam radiotherapy of 28 fractions and concurrent temozolomide (120 mg) six months back. On presentation patient had vision of only perception of light and inconsistent projection of rays in both eyes. On slit lamp examination, anterior segment remained within normal limits with sluggishly reacting pupils. On attempting confrontation test, varying response was seen. Owing to very poor vision and personality disturbances caused by the frontal lobe tumor, visual fields could not be documented. There was no pain on extraocular movement. Fundus evaluation showed established disc edema in both eyes (Figure 1).

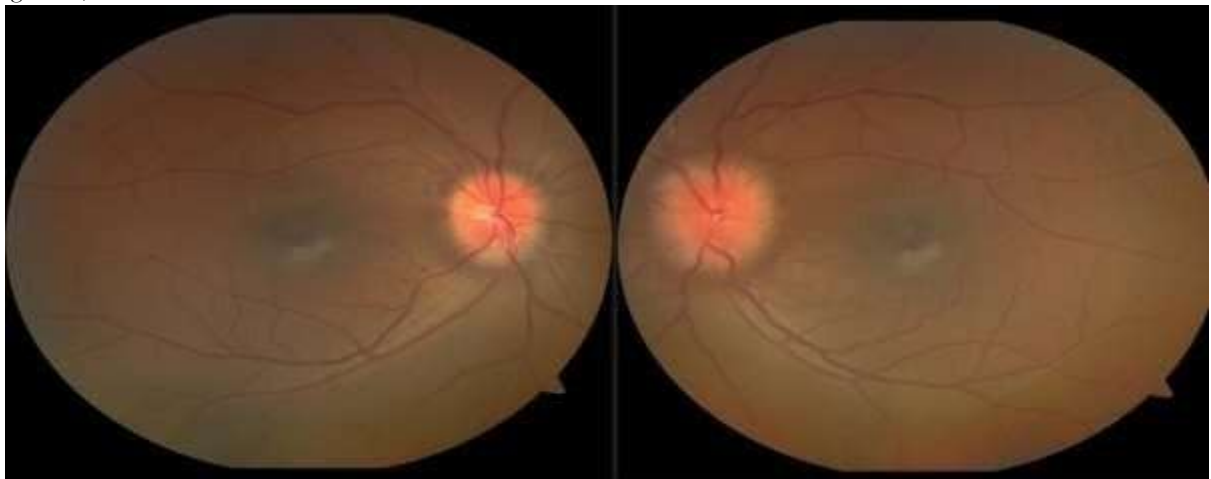


FIGURE 1: Fundus photo showing bilateral disc edema

Suspecting optic neuropathy, MRI brain with orbit was advised. There was mild diffuse thickening of perioptic sheath (maximum thickness ~ 2.5 mm) with subtle postcontrast enhancement (Figure 2).



FIGURE 2: MRI brain showing bilateral optic sheath thickening with post contrast enhancement
Patient was started on IV Methylprednisolone 1gm for 3 days. Optical Coherence Tomography (OCT) of the Retinal Nerve Fiber Layer (RNFL) showed elevated thickness of RNFL layer signifying edema in both eyes(Figure 3). Despite systemic steroids of 1 gram intravenous methylprednisolone given for 3 days followed by oral tapering, patient had no improvement in vision.

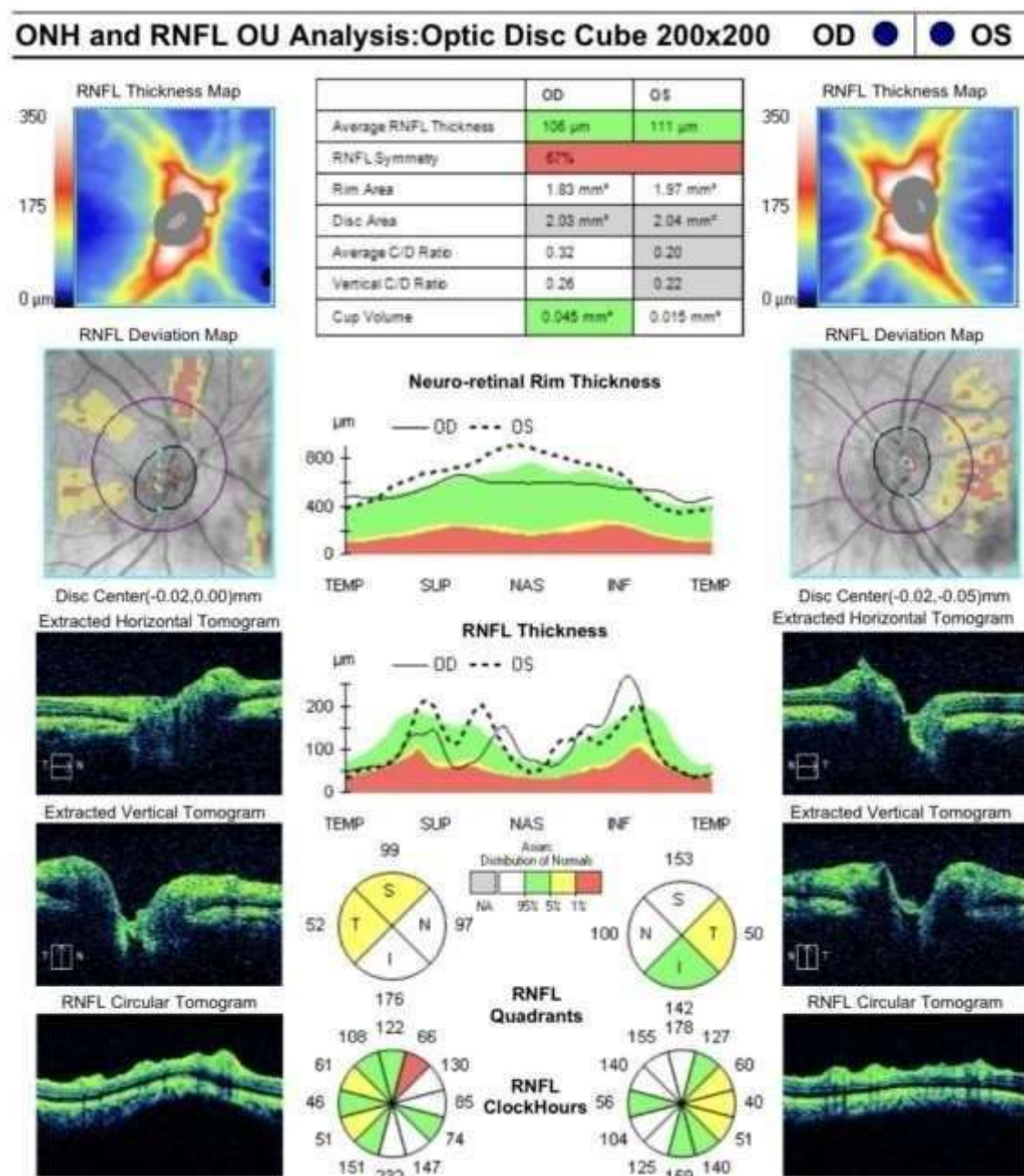


FIGURE 3: Optical Coherence Tomography of the Retinal Nerve Fibre Layer

DISCUSSION

Vincristine, a vinca alkaloid, is widely used in various chemotherapeutic regimens due to its anti-mitotic properties. It is known to cause gastrointestinal disorders, lethargy, alopecia and transient marrow suppression. Neurotoxicity, particularly peripheral neuropathy, is the most common adverse event [8]. It may be sensory, motor or autonomic neuropathy.

Their anti-microtubule activity acts on neoplastic cells to halt mitosis. However the adverse effects on the nervous system are due to damage to microtubules which act as structural components in neurons, unlike other cells of the body. Causing changes to the cytoskeleton of the neurons causes damage to the axonal transport, leading to altered impulse transmission [9]. Further it is known that microtubules play a very important role in the myelinations of nerve fibers [10]. Vincristine thus damages an important effector of

myelination in nerve fibers. A third pathway of neuronal damage by vincristine is postulated to be through reducing the transport mitochondrial calcium channel in the neurons[9].

Optic neuropathy secondary to vincristine is rare, with only isolated case reports in the literature. The pathophysiology is thought to involve disruption of microtubule dynamics necessary for axonal transport in neuronal cells, including retinal ganglion cells, leading to optic nerve dysfunction. Presentation is typically acute, bilateral vision loss with optic disc edema, as in this case. Management centers around timely discontinuation of the offending agent and administration of corticosteroids, though evidence for efficacy is limited. Prognosis is variable, with some cases showing partial recovery, while others remain with permanent deficits.

The following table (Table 1) shows a literature review of similar vincristine induced optic neuropathy case report

Table 1: Literature review of vincristine induced optic neuritis

REFERENCE	AGE /SEX	SYSTEMIC TUMOUR	OCULAR MANIFESTATION	IMAGING MODAILTY	TREATMENT
Norton SW et al., in 1979 [11]	7/F	Acute lymphocytic leukaemia	Unilateral drop in vision and colour vision, Marcus Gunn pupil, amlers grid with central scotoma and normal optic disc and retina	Nil	Maintenance chemotherapy discontinued
Shurin SB et al., in 1982 [12]	15/F	Medulloblastom a	Bilateral visual loss, normal disc and retina	Nil	Vincristine discontinued
Weisfeld-Adams JD et al., in 2005 [13]	6/M	Frontotemporal neuroectoderm al tumour	Bilateral visual loss with bilateral optic disc atrophy (both eye pale disc)	OCT	IV methylprednis olone 500mg BD for 3 days
Woo Hyuk Lee et al., in 2021 [14]	9/M	Burkett lymphoma stage IV group C	Both eye optic disc atrophy (progressed to total pallor)	OCT and MRI	IV methylprednis olone 500mg per day for 5 days

Shurin et al., in 1982 had reported a case of bilateral optic neuropathy following vincristine therapy [12]. Previous or concurrent cranial radiotherapy was claimed to have brought about the side effect which could be plausible in our patient as well, who had received external beam radiation six months prior to the chemotherapy and visual deterioration.

Previous literature on similar cases were almost completely in the pediatric age group.

The most recent report by Woo Hyuk Lee et al., in 2021 [14] spoke about a 9 year old boy progressed to optic atrophy within 3 months of onset of visual complaints. The growing optic nerve of children could be more susceptible to the anti-microtubule activity of the drug. Older age of our patient might have retarded the setting in of atrophy even at 7 months post initiating vincristine therapy.

The onset of visual disturbances post chemotherapy with known neurotoxic agent pointed to a drug induced optic neuritis diagnosis. Absence of other systemic comorbidities and intake of drugs known to cause optic neuropathy deemed the vinca alkaloid as the culprit causing vision drop. Bilaterality of the presentation also sided more in favour of non-infectious etiology.

CONCLUSION

Our report is one of the handful reports documenting bilateral optic neuropathy in the setup of vincristine chemotherapy. It stands out as one of the few reports of vincristine induced optic neuropathy evidenced on MRI. Previous reports were predominantly of pediatric age group whereas ours is an adult presentation. This case highlights the importance of multidisciplinary surveillance for rare but serious adverse effects of chemotherapy and the need for oncologists and ophthalmologists to work closely in such settings. Vincristine-induced optic neuropathy, though infrequent, is a sight-threatening complication in patients receiving the PCV regimen. Awareness, prompt identification, and early intervention are crucial to minimize the risk of permanent vision loss. Further research is needed to establish optimal preventive and therapeutic strategies. We suggest that clinicians need to be alert to the possibility of optic neuropathy in any patient receiving vincristine. Periodic ophthalmologic examinations, including an Optical Coherence Tomography, may facilitate early diagnosis. MRI findings may also aid cinching diagnosis of this optic neuropathy.

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