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Imatinib Related Toxic Optic Neuropathy: Case Report

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Abstract Imatinib mesylate is a chemotherapy medication. With its use, reversible serious ocular side effects, such as optic neuropathy, retinal edema, etc. have been rarely reported. We report two contrasting presentations of imatinib induced bilateral optic neuropathy. In one case, early diagnosis and withdrawal of the drug averted significant visual loss; while in the other case, advanced bilateral optic atrophy ensued due to the late presentation. To conclude, sight threatening optic neuropathy in patients on imatinib therapy, is a possibility. It may not be necessarily reversible and warrants early discontinuation of imatinib.

Keywords: *imatinib, toxic optic neuropathy, optic disc edema*

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1. Introduction

Imatinib mesylate has been found to be effective in malignancies, like hematological and gastro-stromal tumors [1]. It is a well-tolerated medication, but anecdotal adverse events are known to occur, including retinal and optic disc edema (Table 1) [2-8]. It's propensity to cause tissue edema is believed to be due to the inhibition of platelet derived growth factor (PDGF) receptors, thus affecting the fluid regulation in the retinal ganglion cells and leading to their apoptosis [7]. Herein, we highlight two patients with imatinib related bilateral toxic optic neuropathy. In one case, early detection averted significant optic nerve dysfunction, while, the other case developed advanced optic atrophy, due to the late presentation, hitherto unreported so far.

Table 1. Reported Adverse Events Related To Imatinib Mesylate [2-8]

Ocular	Systemic
Periorbital edema	Myalgia
Epiphora	Peripheral limb edema
Extraocular muscle palsy/Ptosis	Fatigue
Blepharo-conjunctivitis	Nausea/cramps/diarrhea
Neovascular Glaucoma	Muscle/Bone pain
Retinal Edema	Rash
Optic disc edema	
Optic Neuritis	

2. Case Report

2.1. Case 1

A 41-year-old Indian woman presented with 3 weeks history of foggy vision in both eyes (Dec 2017). She was on tablet imatinib (400mg/day) for the past one month, status-post gastro-stromal tumor resection. Besides, she was neither on any concomitant medications, nor had any systemic ailment, including diabetes and hypertension. Her best-corrected visual acuity (BCVA; Snellen vision chart) was 6/6 parts both eyes, with normal color vision (36/36 both eyes) and fairly brisk pupillary reactions both eyes (no RAPD). Her anterior segment findings were unremarkable. Positive fundus findings included mild optic disc edema (ODE, Frisen grade1, both eyes) with disc hyperemia, especially in nasal quadrants [Figure 1, a, e]. Her visual fields and visual evoked potential (Right eye latency 102 milli second; Left eye latency 108 milli second) were unremarkable. Optical coherence tomography [OCT; RTVue (software version 6.3); Optovue Inc., Fremont, CA] confirmed disc edema. [Figure 1b, f]. Her brain and orbital contrast imaging did not reveal any space-occupying lesion or evidence of inflammatory/infiltrative optic neuropathy. Additionally, there was no radiographic sign of raised intracranial pressure (ICP) or cortical venous sinus thrombosis (CSVT), with normal cerebrospinal fluid opening pressure (CSF OP of 16 mm H_2O) and normal CSF cytology. Suspecting toxic optic neuropathy, imatinib was

discontinued. After 3 months follow up, there was the resolution of optic disc edema, both clinically and on the OCT (Figure 1, i-p), compared to the initial presentation (Figure 1, a-h). The OCT revealed only subtle partial optic atrophy (R>L; Figure 2, c, k; g, o). Moreover, BCVA of 6/6 OU and normal visual fields were maintained in both eyes. At the last follow-up (Mar 2021), the status quo was maintained (no recurrence).

2.2. Case 2

Another lady, 54 years old, on imatinib therapy (400 mg/day) for chronic myeloid leukemia (CML) for 1 year, was referred for her progressive, diminution of vision since past 6 months (Dec 2019). She was non-diabetic and non-hypertensive. She had BCVA of 6/24 in the right eye, 6/36 in the left eye, with defective color vision in both eyes (Demo plate only). She had pale optic discs with indistinct margins in both eyes. There was gliosis of the optic nerve heads and narrowing of peripapillary blood vessels, suggestive of optic atrophy, secondary to long standing optic disc edema. [Figure 2 a, b]. The visual fields, OCT analysis and VEP indicated advanced optic neuropathy in both eyes [Figure 2 c-h]. Neuro- and orbital imaging ruled out gross pathologies, including metastatic, compressive, infiltrative, or thrombotic lesions. There was no radiological evidence of raised ICP. Lumbar puncture revealed CSF OP to be 20 mm H_2O, with no abnormal cytology. Past routine ophthalmic documentation, done 14 months ago (elsewhere), had revealed BCVA of 6/9parts in both eyes and a normal fundi in both eyes. In the absence of any other obvious cause that could have caused gross bilateral optic neuropathy, the oncologist agreed to stop imatinib. Over the next year, the patient had a stable vision and fundus findings (Dec 2020). Low vision aids were used to visually rehabilitate the patient.

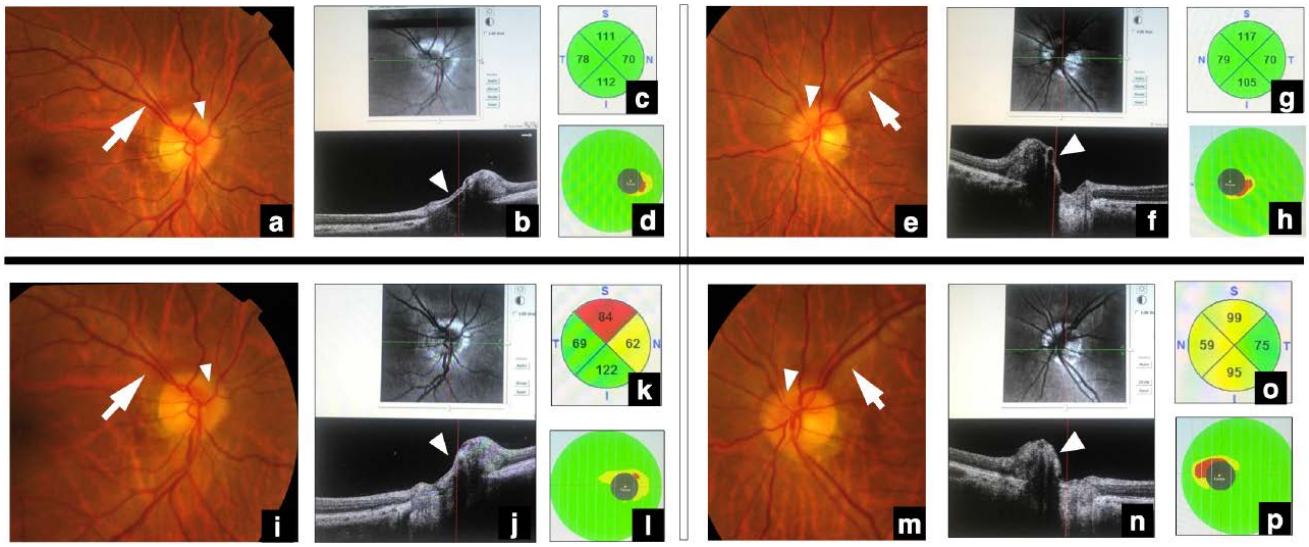

Figure 1. Case 1 findings: On Imatinib therapy- Right eye (RE-panels a-d), left eye (LE-panels e-h): Optic disc edema (ODE) (opacification around blood vessel-white arrowhead) with internal limiting membrane (ILM) striae-white arrow (a,e); True ODE on OCT-white arrowhead (b,f); average peripapillary RFNL in 4 quadrants (c,g); normal GCC thickness (d,h); **After stopping Imatinib**-RE findings (panels i-l), LE findings (panels m-p): Clearing of ODE (baring of blood vessel-white arrowhead) with resolved ILM striae-white arrow (i,m); normalization of the optic nerve head contour-white arrowhead (j, n); relative reduction of RNFL after the subsidence of edema (k,o); Maintained GCC thickness (l,p)

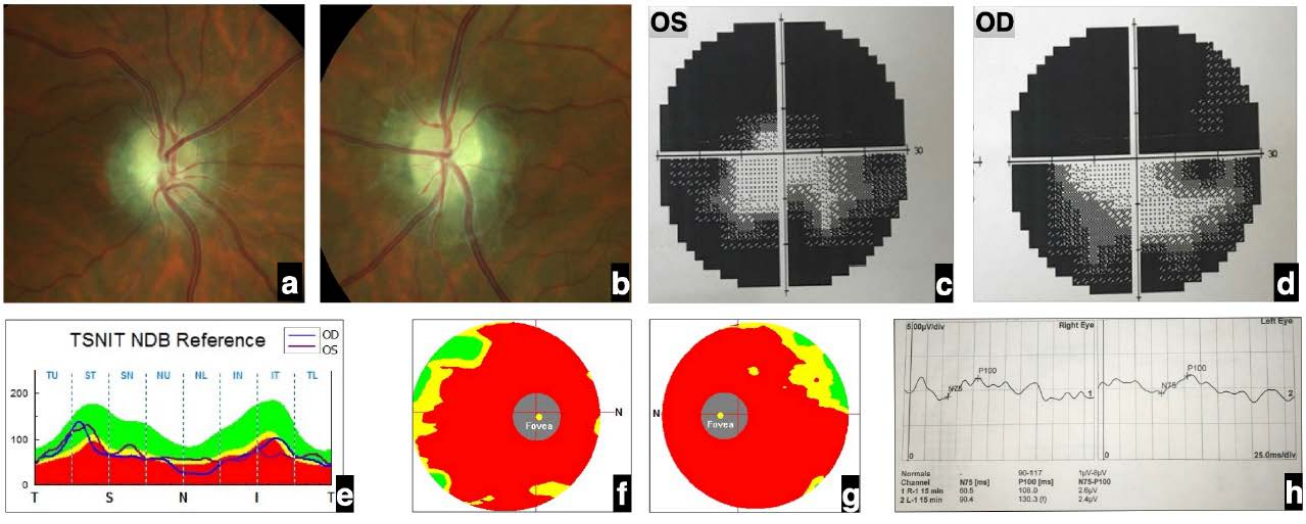

Figure 2. Case 2, Toxic optic neuropathy after imatinib use: Both eyes secondary optic atrophy (RE-a, LE-b); both eyes advanced visual field defect (LE-c, RE-d); OCT reveals RNFL thinning OU (e; LE>RE); OU decreased GCC thickness (f, g); OU Pattern VEP showing decreased amplitudes and prolonged latency in LE (h)

3. Discussion

Imatinib mesylate has rarely been implicated to cause toxic optic neuropathy (Table 2) [3,4,5,6]. In our first case, early diagnosis of imatinib related toxic optic neuropathy helped in the resolution of optic disc edema and preservation of visual function. In the second case, late presentation led to advanced secondary optic atrophy. To the best of our knowledge, advanced residual optic neuropathy due to imatinib toxicity has not been reported so far.

Both of our cases had evidence of bilateral disc edema. Systematic work up ruled out raised ICP, inflammatory optic neuropathy or metastatic infiltration of the optic nerves, by lack of contrast enhancement on orbital and brain MRIs [2]. Other differentials, such as inflammatory, ischemic and nutritional optic neuropathies, were ruled out by the combination of fundus findings, the pattern of visual field deficit, OCT findings, VEP findings, along with normal serum levels of vitamin B_{12} and folate levels. As a diagnosis of exclusion, a diagnosis of imatinib induced optic neuropathy was made, in our cases.

Previously, imatinib has been implicated to cause optic neuropathy (Table 2, cases 1-4). All reported cases responded favorably to the withdrawal of imatinib, with reasonable recovery of visual function [3,4,5,6]. However, residual partial optic atrophy has been documented, as was also seen in our series. The onset of toxic optic neuropathy has been early (1-3 months), except for one case (Table 2, case 4). In the case reported by Napolitano et al, mild, reversible optic neuropathy was diagnosed after 9 years of imatinib use [6]. In contrast, our second case developed advanced optic neuropathy, after one year of imatinib use. Late diagnosis may have happened due to a lack of awareness amongst treating physicians and patients, alike. In some previous reports, complications recurred whenever imatinib therapy was restarted (Table 2-cases 2, 3) [3,5]. Fortunately, in our cases, the oncologists refrained from restarting imatinib, as patients were in remission.

Imatinib is a selective tyrosine kinase inhibitor that targets PDGF receptors. The mechanism for the imatinib toxicity may be related to the inhibited PDGF receptors on the pericytes (on the vascular endothelium, retinal ganglion cells and optic nerve) or a combination of the apoptosis of the retinal ganglion cells and the pericytes [1,7]. Imatinib is not normally known to cross the blood ocular barrier, but it has been shown to do so after damage to pericytes. This may occur as primary toxicity after imatinib use or secondary to prior pericyte loss in diabetes or post-operative induced inflammation [7,8].

4. Conclusion

In summary, toxic optic neuropathy should be recognized as one of the visually disabling complication associated with imatinib use. In suspected cases, early discontinuation of imatinib is advisable. However, the optic neuropathy may not be entirely reversible.

Table 2. Documented Cases Of Optic Neuropathy With Imatinib Use [3,4,5,6]

S.No.	Case report/Age/ Gender of patient	Presentation (symptoms/sign)	Duration of imatinib treatment before detection	Management	Outcome/course
1	Kwon etal/14 yr/F	Photopsiae/visual blurring (6/6 both eyes) /Bilateral optic disc edema (ODE)	2 months	Imatinib discontinued; resumed in 2 weeks	Resolution of photopsiae/ODE; Visual acuity stable; Imatinib restarted -no recurrence (6 months follow up)
2	De luca etal/66 yr/M	Left eye visual loss(6/18parts)/Unilateral disc edema/superior visual field constriction	4 months	Imatinib discontinued	ODE resolved with partial recovery of vision (6/9parts) and depressed central visual field; left partial optic atrophy ensued; Imatinib restarted at half dosage-no recurrence (3 months follow up)
3	Babu K G/50 yr/M	Bilateral severe visual loss (Vision Finger counting 2m both eyes) /Normal optic discs (Both eyes retrobulbar optic neuritis)	25 days	Imatinib discontinued; Oral steroids	Partial (6/18 parts both eyes) but significant recovery of vision both eyes; Partial optic atrophy both eyes; Imatinib restarted after 6 weeks-recurrence of visual loss-Imatinib stopped-vision restored.
4	Napolitano et al/62 yr/M	Unilateral visual loss with ODE/Superior and inferior arcuate scotoma	9 years	Imatinib discontinued	Vision restored with resolution of ODE (2 months)/visual field not mentioned; Started on substitute drug-Nilotinib
5	**Our Case1**	Bilateral visual blurring with bilateral ODE	1 month	Imatinib discontinued	Bilateral optic disc edema resolved (3 months) with partial optic atrophy (No disc pallor; Bilateral RFNL thinning); BCVA (6/6 both eyes)and preserved visual fields (39 months follow up)
6	**Our Case 2**	Bilateral visual loss/ Bilateral optic atrophy	1 year	Imatinib discontinued	Persistent but stable visual loss and optic atrophy; Advanced visual field damage (1 year follow up)

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