Uncontrolled neovascular glaucoma – an alarming manifestation of chronic myeloid leukemia on imatinib therapy – a case report and review of literature

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A 45-year-old diabetic male, with diabetic retinopathy and medically uncontrolled neovascular glaucoma (NVG) underwent intracameral bevacizumab followed by trabeculectomy, with controlled intraocular pressures (IOP) post-operatively, OD: 12 mmHg; OS: 14 mmHg. Patient was referred to hematology, where he was diagnosed as chronic myeloid leukemia (CML) and started on imatinib mesylate. Thereafter, he presented with recurrence of neovascularization and vascularization of the bleb along with OS vitreous hemorrhage at 6 weeks follow-up. While he was planned for OS vitreo-retinal surgery, he presented with OD spontaneous hyphema with raised IOP (OD: 38 mmHg, OS: 16 mmHg). He had maintained a tight glycemic control. Following imatinib therapy, there was a rapid progression and recurrence of neovascularization, eventually leading to failure of trabeculectomy OD and bilateral severe loss of vision. Imatinib may be implicated in the worsening of NVG in CML patients, especially with co-existing diabetes and thus, such patients should receive regular thorough ophthalmic evaluation as long as imatinib continues.

Key words: Chronic myeloid leukemia, imatinib, neovascular glaucoma

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Chronic myeloid leukemia (CML) is known to be associated with varied spectrum of ophthalmic manifestations that includes intraretinal, subhyaloid and vitreous hemorrhages (VH), Roth spots, nerve fiber layer infarcts, and papilledema.[1] Sharma *et al*. also described retinal ischemia, neovascularization, hemorrhages, and glaucoma.[2] Imatinib mesylate is the most widely used drug for the targeted therapy for CML. Few reports

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have suggested development of glaucoma in CML patients with imatinib therapy.[3,4]

Case Report

A 45-year-old male, was diagnosed as non-proliferative diabetic retinopathy (non-PDR), with a history of non-insulin-dependent diabetes mellitus for 10 years, well-controlled with oral medications. Both eyes were managed with pan-retinal photocoagulation (PRP). At presentation, his visual acuity was OD: 20/200 and OS: 20/320. Two weeks later, he was referred to our glaucoma clinic with further drop in vision and raised intraocular pressure (IOP) (OD: 52 mmHg, OS: 48 mmHg). Anterior segment examination revealed bilateral neovascularization of iris (NVI) with zippered angle closure on gonioscopy. A diagnosis of neovascular glaucoma (NVG) was established and the patient was started on maximal antiglaucoma therapy. He eventually underwent both eyes intracameral bevacizumab (1.25 mg in 0.05 ml) injection, followed by trabeculectomy + MMC. At 1 week follow-up, IOP in both eyes was12 mmHg with a well-functioning bleb.

Systemic laboratory work up revealed a high total leukocyte count (TLC = 181,220 cells/µl) with increased blast cells (10%). The peripheral blood smears revealed marked leukocytosis with neutrophilia predominant population of myeloid precursors suggestive of chronic myeloproliferative disorder. He was diagnosed as CML by the hematologist and imatinib mesylate 400 mg OD (Imatib Alpha, Cipla Pharmaceuticals, India) was initiated. Owing to the financial constraints, quantitative BCR/ABL analysis could not be done.

The patient failed to follow-up and came 6 weeks after the initiation of imatinib with OS recurrence of florid NVI and vascularization of the bleb and VH with IOP 12–14 mmHg in both eyes. PRP augmentation was done in the right eye. He maintained a tight glycemic control on a customized oral regimen. Later, he underwent OS vitrectomy for non-resolving VH. Three weeks later, he presented with OD: spontaneous hyphema of 3 mm height [Fig. 1] with raised IOP (36 mmHg). Anterior chamber wash was done and maximal antiglaucoma medications were started. However, OD IOP remained persistently high (30 mmHg), for which trabeculectomy was repeated. Patient's IOP eventually stabilized to OD: 12–14 mmHg (no medications) and OS: 14–16 mmHg with timolol BD. The visual acuity at last visit was light perception in both eyes. The patient was on imatinib for the last 5 months, with TLCs in the range of 4500–6100 cells/µl (normal: 4500–11,000 cells/µl). The possibility of the imatinib leading to worsening of NVG was discussed with the treating hematologist. Since the patient responded well with the imatinib treatment, it was decided to continue it.

Discussion

A rapid recurrence of NVI and hyphema with the abrupt rise of IOP, who was otherwise maintaining a good IOP control, was an alarming presentation and it led us to look up the medical literature for a possible contribution of patient's systemic condition. The review of the literature revealed few case reports and articles addressing effects of leukemia and imatinib that can result in glaucoma.[2-7] Sharma *et al*. attributed the leukemic

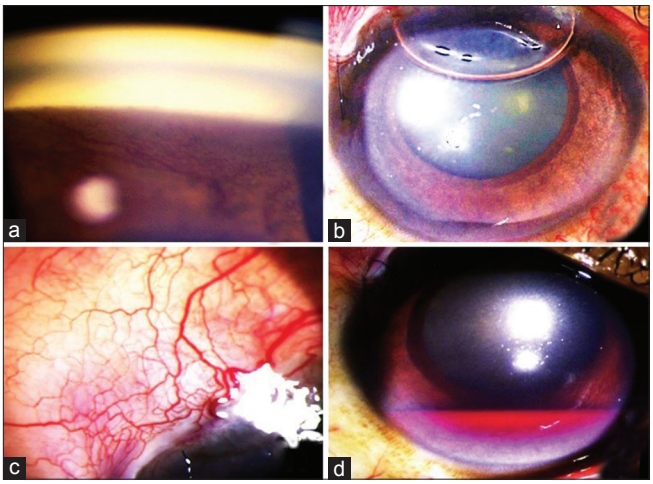

Figure 1: (a) Pre-operative slit-lamp and gonioscopy showing neovascularization of iris (NVI) confirming the diagnosis of neovascular glaucoma (NVG). The patient underwent intracameral bevacizumab injection followed by trabeculectomy with topical mitomycin-C (0.04%) application. (b) Post-operative slit-lamp examination showed well-formed anterior chamber and bleb with regressed NVI. (c) About 9-weeks on imatinib treatment, slit-lamp examination revealed recurrence of florid NVI and vascularization of the bleb along with (d) spontaneous hyphema

infiltration and blockage of the trabecular meshwork, leading to the raised IOP.[2] Figueiredo *et al*. attributed hyperviscosity syndrome associated with CML resulting in retinal ischemia leading to upregulation of vasoproliferative factors including vascular endothelial growth factor (VEGF) and hence, rapid progression in diabetic retinopathy (DR) and NVG.[5] Gulati and Saif reported a non-diabetic 62-year-old male, on imatinib (400 mg OD) for gastrointestinal stromal tumor, developed retinal neovascularization, and hemorrhage after 7 months of initiation of treatment.[6] A dose reduction to 200 mg OD resulted in resolution of hemorrhages without affecting efficacy of drug. They postulated a dose-dependent side effect. El Naggar *et al*. reported a case of a 64 years diabetic female, diagnosed with CML and on imatinib, developed aggressive bilateral NVG within 1 month of initiation of treatment.[7] They proposed that CML induced hyperviscosity had initiated/aggravated retinal ischemia and imatinib may actually have prevented the total vision loss by improving hematologic parameters of patient.

A review of the chain of events in our case brings us to the following possible hypotheses:

1. Imatinib, which is not known to cross the blood-ocular barrier; is able to do so subsequent to damage to ocular/retinal microvasculature. This may occur post-trabeculectomy and also secondary to diabetes mellitus in which loss of pericytes allows imatinib to enter the ocular milieau.[8] It may also occur subsequent to inflammation caused by various ocular interventions
2. Though rare, imatinib can cause a leucocytoclastic vasculitis-like picture wherein the effect on the retinal vasculature is apparent early on due to immediate visual symptoms
3. In DR, the effects of CML in terms of hyperviscosity and anemia can further precipitate ocular ischemia dramatically. However, the temporal sequence of events and the fact that

patient's TLC and hemoglobin levels were within normal range; make this hypothesis unlikely in this case
4. Dose-dependent toxicity of imatinib has also been proposed to cause the retinal neovascularization and hemorrhage. However, progression within weeks in our case rules out dose-dependent adverse reaction.

Conclusion

To summarize, it is apparent that patients of CML are at a high risk of loss of vision due to development of NVG as well as retinal involvement. While CML itself seems to be main culprit, the role of imatinib cannot be ruled out. Though there are several proposed hypotheses, the exact mechanism of imatinib-nduced progression of NVG is not known. However, it is worth noting that CML patients on imatinib therapy should have regular thorough ophthalmic evaluations, especially if diabetic.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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